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ADVANCES IN AGING RESEARCH

HEARING

BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

ONE HUNDREDTH CONGRESS

SECOND SESSION

WASHINGTON, DC

MAY 11, 1988

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ADVANCES IN AGING RESEARCH

WEDNESDAY, MAY 11, 1988

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The committee met, pursuant to notice, at 9:45 a.m., in room G50, Dirksen Senate Office Building, Hon. John Melcher (chairman of the committee) presiding.

Present: Senators Melcher, Grassley, Domenici, Pressler, Durenberger, and Chafee.

Staff present: Max Richtman, staff director; Bill Ritz, communications director; Holly Bode, professional staff; Jennifer McCarthy, professional staff; Kelli Pronovost, hearing clerk; and Kimberly Kasberg, minority professional staff.

OPENING STATEMENT BY SENATOR MELCHER

The CHAIRMAN. The committee will come to order. Good morning.

We are embarking on a hearing that has great potential for older Americans and older people throughout the world. This is a hearing focusing on aging research. What are we looking for in aging research? What is it?

My definition is that it is medical research for health conditions that plague the elderly. The life expectancy in this country in 1900 was 47. Life expectancy in 1983 was for men 71, and for women it was 78. Congress has been grappling over the past year or two with catastrophic coverage for the health of the elderly. What are we doing about long-term health care?

Let's just look at one aspect of this, Alzheimer's. We are told that there are approximately 2.5 million people in America that are afflicted with Alzheimer's disease. It is conservatively estimated that it costs $50 billion a year to care for people afflicted with this disease. Yet there is only about $60 million in funding for research into Alzheimer's disease and other dementias at the National Institutes of Health. That seems very low, compared to a $50 billion annual price tag.

Health care in the United States is estimated to cost about $550 billion this year. Since this is an area where inflation probably takes its biggest toll, we can expect health care costs to be higher next year, and the year after, and the year after that.

This morning we are going to be enlightened. We are going to hear from scientists specializing in problems of the aging, leaders in research from this country, some from abroad. We are going to hear not only about Alzheimer's disease, but about research on the

aging immune system, the regenerative powers of the brain, and the unique nutritional needs of the elderly. We will be instructed on how difficult it is to diagnose Alzheimer's, and perhaps learn what we can hope for in the future regarding this disease.

Overall what we're after is: What hope is there for improved quality of life among the elderly? Can we look forward to some reassurance that the elderly are going to enjoy life more? What can we expect to do at age 80 and older that is relaxing, rewarding and enjoyable? In general, how are we going to make it better for the elderly?

[The prepared statement of Senators John Melcher, John Heinz, Larry Pressler, and John Chafee follow:]

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

OPENING STATEMENT

SENATOR JOHN MELCHER
Chairman, Senate Special Committee on Aging

May 11, 1988 hearing

ADVANCES IN AGING RESEARCH

Good morning. On behalf of my colleagues on the Special Committee on Aging, I'd like to welcome everyone to this morning's hearing on advances in aging research. We are fortunate to have with us today some of the world's most prominent aging researchers, who will be testifying on issues ranging from the prevention of Alzheimer's disease to the role of nutrition in the health and well-being of the elderly to possibly reversing the aging process.

Today's hearing will focus on the United States' search for an aging research policy. Because "aging" as we think about it today is a relatively new concept -- life expectancy at the turn of the century was 47 years at birth, compared to 71 years for men and 78 years for women in 1983 -- we are still looking for answers to the myriad questions raised by an aging society. We in Congress are beginning to consider the issue of catastrophic illness and long-term care, as well as a number of other aging-related concerns, such as reform of Part B of Medicare and pension reform. However, we lack a cohesive biomedical research policy.

The elderly's health bill in this country amounts to an estimated $145 billion per year, which is about one-third of our total health care expenditures. Yet our investment in basic biomedical research into the causes and cures of chronic disabilities and diseases is less than 1 percent of that amount. This occurs despite the fact that results from biomedical research could directly decrease health care expenditures, as well as improve the quality of life for many frail older Americans.

If there are no new breakthroughs in aging research by the middle of the 20th century, we could face more than three times the number of hip fractures, four times the demand for nursing homes, and eight times more dementias than in 1980. Research into Alzheimer's disease and related dementias provides a startling example of the implications of this situation.

The cost of caring for those afflicted with Alzheimer's disease is approximately $50 billion annually. In contrast, total federal funding for research into dementias at the National Institutes of Health in 1987 was only $60.7 million. Because Alzheimer's disease is nearly impossible to diagnose, it is difficult to know how many individuals are affected by the disease, although it is estimated to be about 2.5 million. We do know that the prevalence of dementia increases with age -- only 2 percent of the population between the ages of 60 and 70 have severe dementia, whereas 20 percent of the population over age 80 is affected. We all know the elderly population in the United States is growing, with the over-85 population expected to double by the turn of the century. By that time, the elderly could consume up to one-half of every dollar spent on health care -- unless we move to do something about it.

Problems cannot be solved simply by throwing money at them. This hearing is being held to start a discussion, to help us outline our priorities with regard to the issue of aging research. We are on the threshold of many remarkable discoveries in this area, several of which will be discussed today -- but they cannot be made without our support. I look forward to the testimony of today's witnesses. I am confident that they all will shed light on what can be a complex and technical issue. Advances in aging research are of the utmost importance to Americans of all ages and to the Members of this Committee.

NEWS FROM
SENATOR JOHN HEINZ
SPECIAL COMMITTEE ON AGING
Senate Hart 628 Washington, D.C. 20510-6400 (202) 224-1467

OPENING STATEMENT
ADVANCES IN AGING RESEARCH

SENATOR JOHN HEINZ, RANKING MEMBER
MAY 11, 1988

Good morning.

I commend the Chairman for convening this hearing on the important topic of biomedical research into the aging process and ailments of the elderly.

Since 1900, life expectancy for an American has risen from 47 years to nearly 75 years of age. This remarkable achievement is due to the tremendous strides made in the field of medicine during the past 88 years. Indeed, medical science has practically eliminated 5 of the 10 leading causes of death from the list since the beginning of the century, including tuberculosis and diphtheria. However, longer lives means a new set of challenges for medical researchers. Having succeeded in controlling the infectious diseases which plagued the early 20th century, today's researchers are working on the puzzles of cancer, Alzheimer's disease, heart disease and osteoporosis.

An equally pressing challenge is providing for quality and productive aging. Our over 65 population is projected to double from 11 percent in 1980 to a full 22 percent of the total population by the year 2050. In 1984, the 12 percent of the population over 65 accounted for 35 percent of the nation's health care expenditures. It is expected that the elderly's expenditures for health care will soon reach 50 percent of the nation's total. With this rapid growth in our elderly population, medical researchers are in a race with time to offer hope that senior years need not be characterized by chronic infirmities and pain. Indeed, recent years have seen the shattering of many myths about aging. We now know that healthy people over 65 can be every bit as active and productive as their younger counterparts.

Today, we will hear from some of the leading researchers in the field of aging. Among this distinguished group is David Kritchevsky from the Wistar Institute in Philadelphia. Dr. Kritchevsky, welcome.

Statement Of Senator Larry Pressler
before the
Senate Special Committee on Aging
Hearing on

Advances In Aging Research

May 11, 1988

Mr. Pressler: Mr. Chairman, I commend you and your staff for recognizing the importance of aging research. In an era of huge federal deficits, too often policy makers view research as a low priority. Many view it as a "necessary evil." I hope that today's hearing will dispel these false beliefs.

Life expectancy has increased during the 20th Century as a result of advances in medical research. Medicine conquered premature childhood illnesses and infectious diseases. However, increased longevity has a downside. Quality of life during retirement years may be reduced by multiple chronic conditions. Many elderly will be afflicted with disabling chronic conditions, such as arthritis, dementia, hip fracture, blindness, and incontinence.

We must not be shortsighted. By the end of this century, the total number of persons over 65 will double in size. By the year 2030 the number of people over age 85 will at least quadruple. Aging research can discover new medical interventions to reduce the devastating impact of chronic conditions. By increasing the number of disability-free years, quality of life can be enhanced for our growing older population.

Without new breakthroughs in aging research, we could have three times the number of hip fractures, four times the demand for nursing home care, and eight times more dementias than in 1980. This can be translated into both human suffering and increased federal, state and private sector expenditures for health care. By the time the "baby boomers" reach their mid-sixties after 2010, it is estimated that they will account for over one-half of the demand for health care.

The United States is still in search of a national policy on aging research. When compared to the 12 Institutes of Health, the National Institute on Aging (NIA) is considered next to last in budget priority. NIA is able to fund only 24 percent of the grants recommended for funding following peer review.

It is time for aging research to be a more prominent item on our public policy agenda. I support increased funding for biomedical research and urge policymakers to look at the long-term benefits instead of the short-term cost.

It is amazing to me that only $67 million is spent on Alzheimer's related research when the cost of care to victims of Alzheimer's disease is more than $50 billion annually.

Even though the federal government spends more than $100 billion per year for health care of those over 65, only one percent is spent on biomedical research. With an aging population, biomedical research is even more important to educate and train geriatric practitioners who will take care of our nation's elderly.

Mr. Chairman, I appreciate this opportunity to present my views on aging research and I recognize the efforts of our distinguished witnesses. In their individual endeavors, each contributes to biomedical research and ultimately to the quality of life of our nation's elderly.

STATEMENT BY
SENATOR JOHN H. CHAFEE

Mr. Chairman, I want to thank you for holding today's hearing on advances in aging research and I want to commend you for bringing attention to the need for continued progress by the scientific community in finding cures for the host of diseases that affect our elderly population.

As you know, Mr. Chairman, the demographics of our population are changing but our health care system has not yet adjusted to those changes. Americans are living longer in part because of medical technology developed in the last 50 years. The medical miracles of yesteryear are now common practice. They allow us to keep our loved ones alive longer than anyone two centuries ago would have imagined. Yet, they are expensive. We still need to develop a health care system that can not only pay for this life sustaining technology but also pay for the development of NEW cures and medical practices.

It is amazing to me that in the age of nuclear weapons and men on the moon, we still have no outright cure for cancer. One in three people will be diagnosed as having cancer this year, and one in four will die from it. But with cancer, so often there is at least some hope with radiation treatment, chemotherapy, and experimental drugs. With Alzheimer's disease and other dimenting diseases however, which mainly affect the elderly, there is no prevention and there is no cure.

The federal government spends only 1% of it's $100 billion health care outlays on biomedical research. Our hope is that members of our scientific community, including those testifying today, will someday find a cure to Alzheimer's, to cancer, and to the many other diseases that affect our senior citizens. But, to accomplish this, they need Congressional support. Savings lives, and in the process saving federal expenditures on health care for the elderly, depends on continued progress in aging research.

Mr. Chairman, I look forward to an educational hearing. I am certain that our witnesses will be able to shed some light on the importance and future of aging research.

The CHAIRMAN. Senator Grassley.

STATEMENT BY SENATOR CHARLES GRASSLEY

Senator GRASSLEY. Yes, Senator Melcher. I want to thank you, Mr. Chairman for this very important hearing and for your leadership. You've had a whole series of very important hearings this year; I think you need to be complimented for that. I do have an opening statement.

I want to say that it is a pleasure to attend a hearing that focuses on the progress and advances that we are making. The hearings we convene here in the Congress usually dwell on the problems we face and, more often than not, leave us with the impression that, if anything, we are falling behind in our efforts to deal with them. Although the problems that can afflict older people remain daunting, it would certainly appear that we are making progress through our research efforts.

It is gratifying to be able to say this, because most of us are aware of the cost to the country, and to individuals and their families, of many diseases found in greater degree among older people. I am certainly able to associate myself with the Chairman's remarks on that point.

Alzheimer's disease and osteoporosis are two very good examples. While I was chairman of the Subcommittee on Aging of the Committee on Labor and Human Resources in the 98th and 99th Congresses, the subcommittee undertook projects on both of these subjects. In the course of doing them, it became clear that the burden of just these two diseases is really quite astonishing. As Chairman Melcher mentioned it is estimated that the cost of caring for those with Alzheimer's disease is at least $50 billion annually.

It is estimated that the total cost of osteoporosis and associated fractures in the United States is $7 to $10 billion annually. Osteoporosis is a very widespread problem, even in a farm State like my own, where one would tend to assume that osteoporosis could be less of a problem. I learned from Iowa researcher, Mary Fran Sowers, that some 50 percent of women 68 years of age and older in Iowa have a bone mass level that places them at risk of fracture.

In the face of such diseases as Alzheimer's and osteoporosis which are common in old age, and especially in the face of the great increase in the numbers of older people in our society which will occur when the Baby Boom generation reaches old age, I think most of us look with hope and anticipation to our research community for the help they can eventually bring to eliminating or reducing the burden these diseases cause.

Of course, should our research efforts simply extend the duration of life, without at the same time maintaining its quality, they could simply be compounding the problems we face down the road. Our goal should be to achieve extended life with a reduction in the period of physical and functional decline experienced by those who are living longer. If we can achieve this, then truly our efforts will very definitely have been worthwhile.

And, in that connection, I certainly agree that we here in the Congress should try to achieve an adequate level of support for the kind of promising research that we will have described today.

Thank you, Mr. Chairman. I want to point out for the people who are in the audience, particularly Dr. Bush, as well as others, that Congresswoman Snowe and myself, together with the National Institute on Aging and the National Institute on Arthritis, are sponsoring a set of short research reports on osteoporosis on Friday morning, from 9:30 a.m. until 11 a.m. in room S. 207 at the Capitol. The emphasis will be on international aspects of osteoporosis. My staff placed a flyer with the details about the briefing on the table outside the auditorium.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Grassley. Our first witness today is Mr. Dan Perry, who is the Executive Director of the Alliance for Aging Research.

Mr. Perry is an excellent witness to open this hearing as he can give us an overview of the current status of aging research in this country. Welcome to the committee. We are anxious to hear your testimony.

STATEMENT OF DANIEL PERRY, EXECUTIVE DIRECTOR, ALLIANCE FOR AGING RESEARCH, WASHINGTON, DC

Mr. PERRY. Good morning, Chairman Melcher and Senator Grassley. Thank you very much for the opportunity to appear and testify before you at these hearings.

My name is Daniel Perry. I am Executive Director of the Alliance for Aging Research.

It is becoming absolutely clear that our Nation is headed toward a crisis due to the rising cost of health care and long-term care for our people. The total spent by Americans for health care this year, as the Chairman has pointed out, will be more than $550 billion. And, as the Chairman mentioned, because this is the most inflationary sector of our economy, the bills will be far higher next year, and the year after that.

The members of this committee know that the "graying of America" is a significant factor. One-third of U.S. expenses for health care are spent on the 12 percent of our population that is over 65 years of age. By the year 2000, older Americans will consume one-half of a much higher health bill.

We all know what comes after that. In the first few decades of the new century, the Baby Boom will become the Senior Boom. If there are no changes in the way people age by the middle of the coming century, we could have more than three times the number of hip fractures, four times the demand for nursing homes, and eight times more dementias than in 1980.

Medical costs for the care of a vastly greater number of older persons could overwhelm our entire health care delivery system. How do we avoid this dilemma? I suggest that our options are really few.

We can continue to pay the bills. We will simply drain national resources from all other priorities, sending more dollars after ever more costly and often inefficient health care.

We can choose to ration health care using age as the criterion for denying medical care to people beyond a certain age. Shocking as it is, this option is being urged upon us by some medical ethicists and

others. They believe that age-based rationing is both justifiable and inevitable.

Of course we can ignore the problem until a later Congress, a later generation. Or we can take the sort of action that I believe is more in keeping with this committee's best aims and purposes. We can set a national goal to stimulate scientific research into the underlying causes of diseases and disabilities that afflict millions of older persons.

As little as one-half of one percent of that $150 billion, Mr. Chairman and Senator Grassley, that we spend on treating the conditions of aging—if that fraction were applied forcefully and effectively to research, it could propel us toward preventions and cures for many disabilities that place a crushing cost burden on individuals, on families, and on taxpayers.

Research into human aging, if properly supported, could lead to breakthroughs well before the Baby Boom becomes the largest Medicare generation in history.

Are our scientists ready for this? This is the question for this morning. Have researchers reached the point at which interventions into aging are indeed plausible? Can we really expect that investments in aging research will soon produce dramatic changes in how we experience old age?

Mr. Chairman, I invite this committee to consider these questions as it listens this morning to the following witnesses.

Those who are about to testify before your today represent some of the most promising scientific researchers in the world. The idea that we might soon intervene effectively in our own aging is a startling notion, even to scientists.

You will hear this morning from scientists whose experiments have restored youthful resistance to infections and disease in patients whose immune response have been worn down by old age.

You will hear that very soon older women in the United States may routinely receive a safe and effective hormone replacement therapy that could greatly lower their risk to both heart disease as well as to crippling osteoporosis.

You will hear that what we eat, and especially how much we eat, may be a key controlling factor in the rate at which we age.

You will hear of the latest progress against Alzheimer's disease. Until just recently, it was assumed that the drastic mental deterioration associated with Alzheimer's was inevitable with age, and irreversible. New information before you this morning suggests that the Alzheimer's puzzle is fast becoming a manageable research agenda.

What you will not hear this morning is a desire to perfect a 150-year-old man or woman; ours is not the pursuit of immortality. As both of you gentlemen so correctly pointed out, ours is the goal of quality of life in later years.

Those who will testify this morning are achieving scientifically sound advances toward fuller, fitter lives for more people within realistic limits.

The goal of modern aging research is not simply extended life-span, but extended health-span, an absolute increase in the number of years free from disease, decline, and disability.

This committee is to be congratulated for guiding us toward a fuller understanding of the potential of aging research. From the work of this committee can come a mandate for placing a higher priority for aging research within this Nation's overall science policy.

We have already heard this morning the figures of Alzheimer's disease. When you factor in the indirect costs, lost productivity from family members and caregivers that take care of the Alzheimer's victim, the total larger cost is not just $50 billion, but $90 billion in costs to our economy.

At the same time, the total investment in finding a cure or prevention for Alzheimer's disease is the $60 million you mentioned, Senator Melcher, from the NIA, and approximately $30 million more across various other agencies. We have a ratio of $90 billion on one side of the ledger and $90 million on the other.

That is a cost versus prevention ratio of 1,000 to 1. It simply is not a rational response on behalf of an aging society.

The Alliance for Aging Research looks beyond today's hearings to working with the chairman and members of the committee, and with its staff, to help fashion a more effective research strategy for our aging society.

Thank you very much. I would be happy to answer any questions.

The CHAIRMAN. Thank you, Mr. Perry. Can you compare the amount, the quality, and the types of biomedical research policies we have in this country for the elderly with other industrialized nations around the world?

Mr. PERRY. I would say, Senator Melcher, that the quality of the research in this country is second to none. I think the United States is the world leader in biomedical research. We have a great deal to be proud of in our National Institutes of Health.

I believe that aging research, as a governmental and national priority in terms of its funding, probably does lag behind some of the other nations of the industrialized world that are experiencing very similar aging demographics to our own, notably Japan. In their Year 2000 Report, the Economic Planning Agency of Japan cited the aging of the Japanese society as the number one domestic priority for the 21st century.

Certainly that should be echoed and, in fact, we should be saying much of the same in this country. That includes a strong commitment to basic research, clinical practice, education of geriatric practitioners, and psycho-social research. I think that some other countries have shown us the way when we indeed should be leading. Our scientists, however, are the best.

The CHAIRMAN. You mentioned the Baby Boom in your testimony. When does the Baby Boom become the Elderly Boom? Is it about the year 2000?

Mr. PERRY. The oldest of the Baby Boomers are those who were born in the year 1946. If we go by the standard definition of 65 as the beginning of retirement age, or older age, then we are looking at the years 2010 to 2015 that the Baby Boom begins to be the generation eligible for Medicare. It begins after 2010.

By the year 2040, they will be at their peak numbers among the aged. Even the younger members of the Baby Boom generation will be past 65. Our population of the oldest old, those in greatest need of medical care because we are still waiting for those breakthroughs in research, will have quadrupled by the year 2040.

The CHAIRMAN. And that takes into consideration that the life expectancy may continue to climb?

Mr. PERRY. Yes, sir. The life expectancy will increase. It will climb. Our real threat is the increasing disability and chronic diseases which we now know occur in greater frequency among people in their 70's and 80's. As that population increases, the statistical curves on hip fractures, osteoporosis, osteoarthritis, dementia, incontinence, etc. just go right off the chart; that should be the target of very much of our research—interventions in those areas.

The CHAIRMAN. Interventions in dementia are particularly important?

Mr. PERRY. Dementia, osteoarthritis, osteoporosis—mobility problems—and incontinence, which is a cause for a great number of people being committed to institutional care.

The CHAIRMAN. Thank you.

Senator Grassley.

Senator GRASSLEY. Yes. Thank you Senator Melcher, Mr. Chairman.

First of all, you didn't take much of the opportunity you had here to tell us a little bit about what the Alliance itself is doing on aging research. I know that the main point of this meeting is to hear from the researchers themselves. Having had some connection with the organizing of your group when it first started—a very modest effort on my part, but I was glad to help out—I think you ought to take a little bit of time, just to tell us what you might be doing along that line.

Mr. PERRY. Thank you very much for that question, Senator. Indeed, Senator Grassley, you were very important to our efforts just 18 months ago when this organization was established as a means to link decisionmakers more closely with what is progressing in the scientific community, and I thank you for that.

In the recent months, we have joined forces with many of the other health and aging organizations on a national basis, the Heart Association, the Cancer Society, the National Osteoporosis Foundation and many others, to create a professional judgment budget, the amount that could effectively and reasonably be spent to advance aging research in the coming fiscal year. That document has been published and is now being circulated here in Congress. I would be happy to share a copy of this with the members of this committee and its staff.

In this we analyze what is going on at the National Institute on Aging, the Arthritis Institute, the Neurological Institute and the Veterans Administration. We don't often think of that as key to aging research, but indeed the VA conducts a great amount of our geriatric education and training.

We have analyzed what the Federal Government is doing in aging research, and we have proposed some budget figures and

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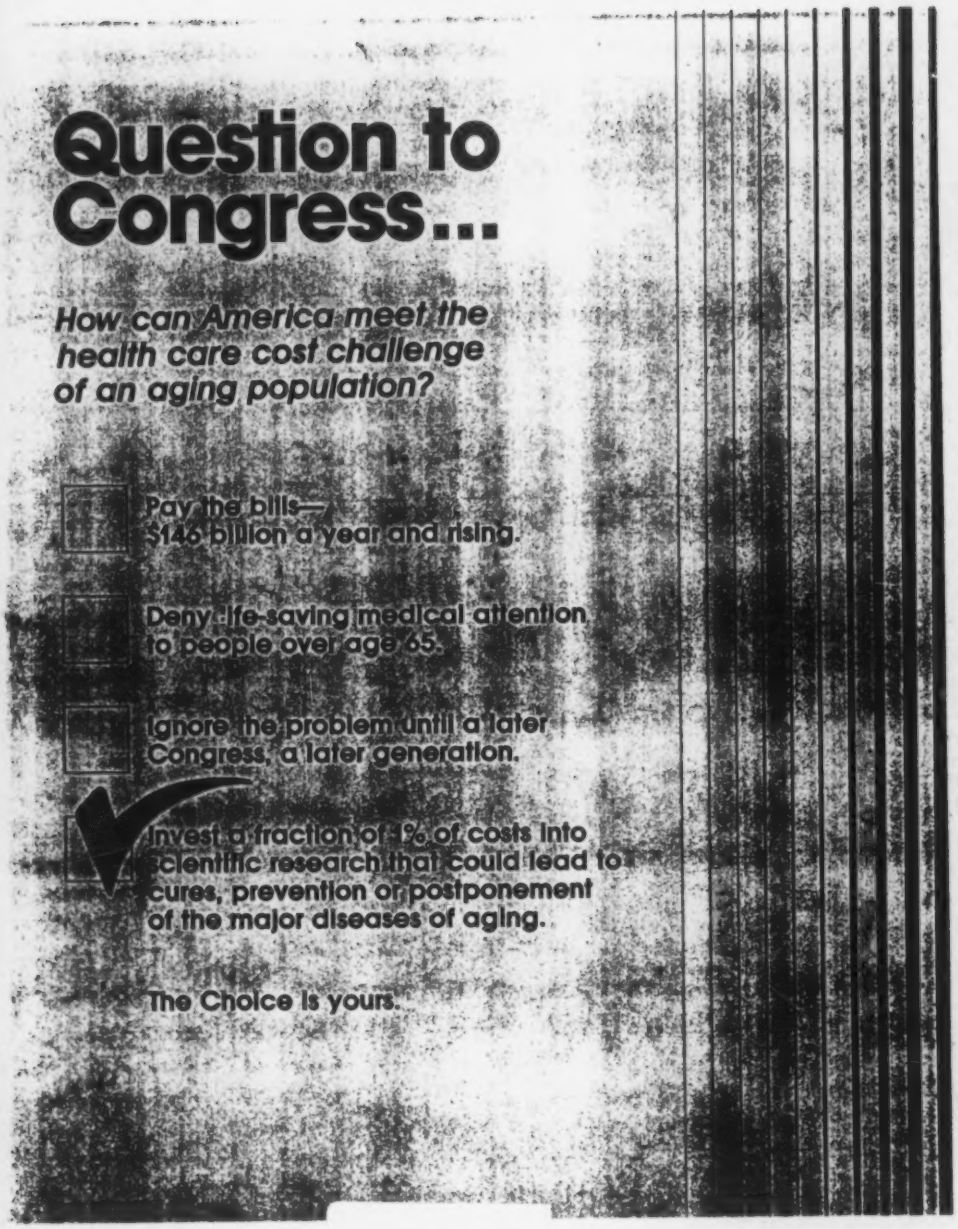
other suggestions that could lead us to a greater chance of breakthroughs in the near term.

The CHAIRMAN. Without objection, that document will be made part of the record at the conclusion of your remarks.

Mr. PERRY. Thank you Senator.

[Information to be supplied follows:]


Question to Congress...
How can America meet the health care cost challenge of an aging population?
Pay the bills—$146 billion a year and rising.
Deny life-saving medical attention to people over age 65.
Ignore the problem until a later Congress, a later generation.
Invest a fraction of 1% of costs into scientific research that could lead to cures, prevention or postponement of the major diseases of aging.
The Choice is yours.

Opportunities for Aging Research in the Fiscal Year 1989 Budget

Prepared by the

TASK FORCE FOR
AGING RESEARCH FUNDING

Alliance for Aging Research (1988 Chair)
Alzheimer's Disease and Related Disorders Association
American Cancer Society
American Diabetes Association
American Geriatrics Society
American Heart Association
Institute for Advanced Studies in Immunology and Aging
National Committee for Research in Neurological
and Communicative Disorders
National Foundation for Long Term Health Care
National Osteoporosis Foundation
Paralyzed Veterans of America

Washington, D.C.
May 1988

Aging Research: An Investment for a Nation Growing Older

As a nation we are going to have to make choices about how to meet the increasing health care costs for an aging population. We can continue to pay the bills. Last year, an estimated $146 billion was spent on health care for people over age 65. We can go as far as rationing to deny life-saving medical care to people over a certain age as some have recently suggested. We can just ignore the problem and watch health care spending consume an even greater share of our gross national product. Or we can invest a fraction of 1 percent of all health care spending into research which could lead to breakthroughs that would eliminate much of the need for many costly medical procedures, hospital stays and long term care.

A greater investment in aging research today will greatly improve our nation's ability to meet ever-increasing health care costs for tomorrow.

Our national health care bill approaches one-half trillion dollars a year. The elderly, currently only 12 percent of the total population, already account for about one-third of the demand for health care which costs the nation over $450 billion this year alone. By the year 2000, it is estimated that older Americans will consume one-half of an even larger health care bill for the U.S. By the year 2030 -- when the baby boom becomes the senior boom -- federal expenditures for health care as a percentage of the gross national product will have more than doubled from where they are today.

The need to act is clear. More people are living longer than ever before. It is estimated that the number of Americans over age 85 -- currently 2.7 million -- will double by the end of the century and will quadruple in the next 60 years. Without any medical breakthroughs to prevent disease and curb the costs associated with aging, we will be spending more and more for the treatment and care of older American without the fullest return in increased productivity or in an improved quality of life. We can tinker with changes in the health care delivery system which can produce some savings -- and we should look for savings wherever we can -- but these savings will not equal the long-term benefits of dramatic medical and scientific changes that will alter the way we experience old age.

Overall, we spend an estimated $146 billion a year for the health care of people over age 65, but far less than half of 1 percent of that amount is reinvested in research which could lead to lower health care costs for chronic diseases and disabilities. This represents a poor investment strategy for a nation soon to experience the largest senior boom in history.

A national strategy that places more emphasis on aging research could help lower medical expenses and improve the health of older Americans for decades to come. An effective strategy would include targeted investments in the basic biology of human aging, research aimed at specific diseases such as Alzheimer's, technology transfer to move findings quickly to clinical trials, greater support and training for geriatric medicine, and further study of the psychological, behavioral and sociological aspects of aging. Progress in aging research is already being made but a greater investment is necessary to take advantage of the emerging scientific and medical possibilities that are just beyond the threshold.

At the level of basic research our scientists are learning how cells live and die, and how genes program major body functions. DNA research has the potential for unlocking the many mysteries into what causes the body to decline and become more vulnerable to diseases. One of the most promising opportunities now before the scientific community is the possibility of gaining a fuller understanding of the genetic make-up of the human body. The technology now exists to identify, map and sequence the billions of chemical units to reveal the full range of human genetics. Scientific momentum is now gathering behind a national effort called the Genome Initiative which could accomplish this in the next 10 years. The molecular "road map" into the causes of human diseases and aging could be the most potent tool for research since the invention of the microscope.

Within the next 20 years, many scientists and researchers believe, a better grasp of genetics may provide the means to avert major diseases associated with aging and perhaps to slow-down or modify aging processes for human benefit.

We now have a glimpse of a future which could include the ultimate conquest of frailty, disease and disability that occurs frequently with aging. If we make wise investments in aging research today, we can anticipate a future with a larger elderly population less reliant upon costly surgery, hospital respirators and expensive long-term care. More Americans will find their health and vigor maintained longer with disease and disability reduced to a minimum prior to death. In short, our goal is not just a longer lifespan but an extended "healthspan," helping a greater number of older Americans lead vigorous, more productive lives with less vulnerability to chronic disease.

Significant savings can be achieved. Take Alzheimer's Disease for example. The cost of this disease, afflicting over six percent of Americans over age 65, is enormous. The Congressional Office of Technology Assessment has estimated the direct cost for nursing home care for people with Alzheimer's Disease is as much as $48 billion each year. Total costs to the U.S. economy may be as high as $90 billion. Of course the federal government absorbs more and more of these costs each year through Medicare, Medicaid and other federal health expenditures. There is also a tremendous drain on private health-care dollars, spelling overall higher health care costs for all Americans. Measured against costs as much as $90 billion a year due to Alzheimer's Disease, only about $90 million was budgeted across a number of federal agencies in fiscal year 1988 to find a prevention or cure.

A breakthrough in finding a cure or prevention to Alzheimer's Disease -- once thought a long way off -- is becoming a manageable research project. Researchers are making tremendous progress in locating and identifying one or more genes associated with Alzheimer's Disease. Newer and more powerful imaging equipment has revealed a much closer look at the human brain and the causes and effects of Alzheimer's Disease.

This is just one of the areas where we can achieve great benefit at less cost through aging research. We have the potential to do more. We have the ability and technology to do more. What is needed is a commitment to invest in aging research as a national health priority.

About this Opportunity Budget

Current fiscal constraints place limits on the amount of money available for even the most worthwhile of projects. This budget provides a professional assessment of feasible opportunities for aging research during the next fiscal year. While somewhat limited by tight budget restrictions, the opportunities for aging research presented in this budget will allow us to keep the door open for progress in providing relief to the many maladies associated with aging. These research opportunities will lead to improving the lives of millions of older Americans and more millions to come.

This budget was developed with the advice and consultation of experts in the field of aging research. The principal government agencies conducting aging research -- the National Institute of Aging, the National Institute for Mental Health, the National Institute of Neurological and Communicative Disorders, the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Veterans Administration -- were examined by experts outside of government to develop the budget guidelines presented here. In addition, aging research opportunities conducted by several other government agencies were also examined. Those who helped prepare the following budget and who helped identify current research opportunities were:

-- the Alliance for Aging Research (1988 chair),

-- the Alzheimer's Disease and Related Disorders Association,

-- the American Cancer Society,

-- the American Diabetes Association,

-- the American Geriatrics Society,

-- the American Heart Association,

-- the Institute for Advanced Studies in Immunology and Aging

-- the National Committee for Research in Neurological and Communicative Disorders,

-- the National Osteoporosis Foundation,

-- the National Foundation for Long Term Health Care, and

-- the Paralyzed Veterans of America.

While the data needed to fully assess all the federally-supported health research affecting human aging is not currently available, the following document should be viewed as a bulletin highlighting some of the opportunities which exist at federal agencies most active in aging research.

It is hoped that this budget will provide guidance to members of Congress in the development of legislation that adequately supports and advances progress in aging research during fiscal year 1989. Consideration of national spending priorities by Congress this year is our best opportunity to lay a strong foundation for aging research into the next decade and beyond.

Budget Recommendations

Fiscal Year 1989 Opportunity Budget
for Selected Agencies
(number in millions)

Agency	FY 1988 Allocation	President's FY 89 Request	Opportunity Budget FY 89
National Institute on Aging*	194.7	204.5	260.0
National Institute of Mental Health**	14.6	15.5	26.0
National Institute of Neurological & Communicative Disorders & Stroke*	534.7	571.0	704.5
National Institute of Arthritis and Musculoskeletal and Skin Diseases*	147.0	158.0	224.0
Veterans Admin.**			
A. Medical Research Service Funding	15.5	16.7	18.9
B. GRECCs	12.9	13.8	23.8+

*Figure for total institute funding.

**Represents the amount of agency spending on aging-related research and training.

+Provides start-up funds for four additional centers.

National Institute on Aging

A fiscal year 1989 budget of $260 million for the National Institute on Aging would allow full funding for all 602 of the institute's grantees. If the President's proposed fiscal year 1989 spending level for the institute is enacted, the NIA will be forced to negotiate drastic across-the-board reductions of up to 16 percent for all approved research grants for next year.

At present, the National Institute on Aging is able to fund only about 24 percent of the grants recommended for funding following scientific peer review -- one of the three lowest funding rates for the National Institutes of Health. The funding level recommended in this budget would raise the percent of approved grants that actually become funded to 37 percent of all applications that are judged meritorious by scientific review panels. The 37 percent level would approximate the priority scores that prevailed in the 1987 budget cycle.

Funding the National Institute on Aging at only the level proposed by the Administration for 1989 would have a profound detrimental impact. Here are a select few examples of the many highly-rated research projects which will not be funded as long as only 24 percent of approved NIA projects can be funded:

-- A research project at the Mayo Clinic to test whether certain back muscle exercises can reduce the risk of osteoporosis of the spine.

-- A project from Miami that would carry out work on reducing frailty in some older people by understanding the mechanism of lost strength and coordination, particulary in the arms.

-- Research at the State University of New York at Albany to analyze certain proteins produced by aging cells and to compare them to proteins produced in people who suffer from diseases that cause premature aging.

Additional Opportunities at the National Institute on Aging

To help continue advancements in aging research at the National Institute on Aging, the following are identified as key areas where opportunities for progress exist:

-- **Alzheimer's Disease.** This opportunity budget will allow the National Institute on Aging to create three new Alzheimer's Disease research centers in addition to the 10 that exist now. In addition, there are research opportunities for the early identification of Alzheimer's Disease; further development of needed diagnostic capabilities; and genetic linkage and gene identification.

-- **Biological Processes of Aging.** Some of the most important research opportunities for understanding aging processes now exist at the National Institute on Aging through the use of sophisticated molecular techniques. Using these techniques, scientists have recently identified a protein associated with cell aging, and the gene coding for this protein has been cloned. In addition, the institute has undertaken a new initiative to establish reliable and meaningful biomarkers of aging which can be used to test interventions in human aging within 10 years. Biomarkers of aging are biological measurements which reflect rates of aging in tissues, organs or whole organisms. Funding in this area will help researchers continue to make advances in DNA sequencing and cloning, distinguishing aging processes from disease and establishing a panel of biomarkers of aging.

-- **Nutrition and Aging.** One of the more dramatic findings in nutrition research is that dietary-restriction in rodents, without nutrient deficiency, extends maximum lifespan, retards the onset of many spontaneous late-life cancers and other diseases, and slows the rate of biological aging. Dietary-restriction has been the only intervention that has consistently produced this outcome in mammals. This research opportunity budget will allow National Institute on Aging researchers to use the caloric-restriction model to test the basic mechanisms of aging and investigate whether this effect applies to other mammals including humans.

-- **Training.** The need for greatly increased numbers of people trained in geriatrics and gerontology is clear. Several studies, including a landmark report by the Institute of Medicine, have warned about the shortage of people trained in these fields. A recent study in the New England Journal of Medicine states that we need to at least double the yearly number of graduates in geriatrics to meet the needs of this nation by the year 2000. This budget recognizes that need and supports the National Institute on Aging plans and funding to develop training centers as suggested by the Institute of Medicine.

National Institute of Mental Health

The National Institute of Mental Health's aging research branch is conducting pioneering research into the causes and effects of Alzheimer's Disease. Current funding levels, however, have put 21 highly-rated research projects on hold. The $26 million recommended in this budget will allow the branch to move forward with the projects, including:

-- brain imaging studies in Alzheimer's Disease and late onset schizophrenia.

-- studies in depression.

-- family stress caused by Alzheimer's Disease.

Funding in this opportunity budget will allow for expanded program study in the development of treatment for depression in Alzheimer's Disease as well as exploration in psychosis, anxiety, and health behavior. The increased funding will provide for the addition of a sixth research center to focus on psychopharmacology. This budget would also allow additional funds for research training programs.

National Institute of Neurological and Communicative Disorders and Stroke

Nervous system disorders greatly affect older people. Among the most prevalent of these are Parkinson's Disease, Alzheimer's Disease and stroke. Nearly half a million Americans suffer from Parkinson's Disease, many over the age 60. Two million Americans have severe dementia and as many as eight million have a milder form of the disease. Stroke is the third leading cause of death in the U.S. About 500,000 Americans suffer a stroke each year, with the incidence of stroke more than doubling in each successive decade after age 55. The National Institute on Neurological and Communicative Disorders and Stroke is conducting research into these and other disorders among older Americans.

New drugs and other research activities have tremendous potential in treating and preventing stroke. Low funding levels for the National Institute of Neurological and Communicative Disorders and Stroke would force the postponement of the following clinical trials and other important research activities:

-- Two clinical trials involving the testing of drugs which could dissolve existing blood clots and prevent the formation of clots leading to additional strokes. One test involves TPA (tissue plasminogen activator), which was approved last year by the Food and Drug Administration for use in the treatment of heart attacks. The clinical trial would examine TPA in dissolving already-formed blood clots which can stop blood flow to the brain. The other trial would test the use of heparinoids in preventing the formation of blood clots that can cause additional strokes.

-- Issue a contract for a case-control study to evaluate the risk of brain hemorrhage within 24 hours of the use of thrombolytic therapy (treatment with drugs used to dissolve a blood clot).

-- Establishment of six additional stroke centers to further stimulate the research environment to more clearly define the disease processes in stroke. The research could lead to significant advances in identifying high risk factors and in developing additional methods for the treatment and prevention of stroke.

The institute has a number of studies underway to assess the effects of normal aging on various aspects of the central nervous system. A specific example is in the area of presbycusis -- age-related hearing loss. Evidence suggests that the inner ear and auditory nerve may simply wear out. The microscopic hair cells that line the inner ear and are responsible for the ability to hear high-pitched sounds appear to be the most vulnerable in the auditory aging process. Researchers at the institute are studying the microscopic changes that occur in the inner ear and the affect of aging on the transmission of nerve signals along the auditory pathways in the brain.

Epidemiologic studies indicate that there will be an increase in age-related balance disorders, including vertigo. There is a need to expand basic studies of equilibrium, which utilize recently developed methods of brain imaging and measuring cerebral blood flow, to include the balance disorders of the elderly that often are precursors to falls, fractures and permanent disability.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

More than 37 million Americans suffer from arthritis and related disorders, and 24 million more -- mostly older American women -- have conditions known as osteoporosis. This is a particularly debilitating disease characterized by an exaggerated loss of bone tissue and increased incidence of fracture of the hipbone and wrist. An estimated 1.3 million bone fractures annually are attributed to osteoporosis in Americans age 45 and over. These disorders are the number one crippler of older Americans and severely limit their ability to lead full and vigorous lives. The cost of treating these disorders is high--an estimated $31 billion annually in medical costs and associated economic losses.

Important research to treat these disorders and to improve the lives of older Americans afflicted with these conditions is being conducted by the National Institute of Arthritis and Musculoskeletal and Skin Diseases at research centers around the country. Research on osteoarthritis at Massachusetts General Hospital and at the Stanford University Medical School is showing promising results. New research on osteoporosis conducted at Creighton University in Omaha, Nebraska, has revealed information on the loss of bone from the spine. The research finding will be a critical link to find cures and preventions for this disease now affecting as many as half of all women over age 45 and 90 percent of women over age 75.

Veterans Administration

Today there are almost 4.8 million veterans over age 65. It is predicted that this number will increase to 7.2 million in 1990 and to nine million by the year 2000. The Veterans Administration, the principal provider of health care for many older veterans, is also responsible for a substantial amount of aging research and training in the field of geriatrics. Given the growth in the population of older veterans, increased funding is necessary for the Veterans Administration to stay ahead of the curve in the field of aging research.

This budget includes funds for the establishment of four additional Geriatric Research, Education and Clinical Centers (GRECCs). The centers were designed to increase the basic knowledge of aging, transmit that knowledge to health care providers, and improve the quality of care to the aged. The Veterans Administration is authorized to establish 25 centers. There are currently 10 centers located across the U.S. with two centers in the planning stages. The four additional centers will move us closer to the original Congressional goal for GRECCs in the mid-1980's.

Additional Opportunities for Aging Research

Successful human aging is a research challenge that cuts across traditional barriers between scientific disciplines. As such, several of the twelve Institutes of Health conduct valuable

research on the diseases and processes associated with aging. In addition to the areas already discussed, listed below are some opportunities for much needed advances in aging research.

Genome Initiative. Perhaps no other scientific research project has greater potential for unlocking the many clues to aging than the Genome initiative to map and eventually sequence human DNA. As currently proposed, the budget for the National Institutes of Health includes some funding to begin this important effort through various research grants. While such funding is a positive first step, a more comprehensive and coordinated approach is needed. Other nations, including Japan and the Soviet Union, are already underway with their own Genome projects. In order to maintain this nation's competitive edge in biotechnology and related industries, we need to move ahead immediately with our own coordinated research effort. The National Academy of Sciences has called for $200 million each year for the next 15 years to complete the Genome initiative. This is a realistic estimate of new funding for a project of this scope. The advantages and benefits of undertaking the Genome initiative warrant a substantial investment of our resources.

Cardiac Research. Cardiovascular disease is the leading cause of death among older Americans. The National Heart, Lung and Blood Institute has proposed a clinical trial to determine whether a new class of cholesterol-lowering drugs -- HMG CoA reductase inhibitors -- will reduce death from cardiovascular disease in men and women over age 60. If proved successful, the use of this new class of drugs will be instrumental in helping to save lives and in reducing the need for chronic incapacity, costly hospital stays and long term care. Without additional funding to the institute for fiscal year 1989, the project will be postponed for its second year.

Cancer. Although cancer affects people of all ages, it develops most often in older people. The single greatest risk factor for all cancers is age. The American Cancer Society estimates that 985,000 people will be diagnosed as having cancer this year, and over half will be over age 65. About 395,000 people will die from cancer this year, close to 60 percent of them over age 65.

The National Cancer Institute supports a number of research activities focusing on the treatment of cancer in older Americans. Several areas include:

-- Research at the University of California at Los Angeles and the Veterans Administration Hospital in Sepulveda, California, examining treatment which may adversely affect older women with breast cancer. Most breast cancers occur in women age 65 and over. The researchers have found that doctors are not giving women over age 65 the same vigorous treatment as younger patients. This, researchers fear, may needlessly shorten the lives of older patients.

-- Research at Johns Hopkins University in Baltimore developing new ways to predict the response to hormone therapy in men over age 65 with prostate cancer. The ability to test the response to this treatment will be extremely useful in improving the outlook for patients with advanced prostate cancer.

-- There are a number of additional research opportunities which merit further investigation and funding, including: the effects of chemotherapy on older people; primary care provider education about cancer prevention; treatment protocols for the elderly; pharmacokinetics and drug sensitivity of elderly cancer patients; and quality of life issues for older cancer patients.

Eyesight. Poor eyesight, while not an inevitable consequence of aging, reduces the quality of life for a great number of older Americans. Nearly one-third of all visits to physician offices for medical eye care in the U.S. are made by people 65 years or older. Opportunities exist at the National Eye Institute for important age-related research to:

-- Help identify causes and factors affecting age-related maculopathy, the leading cause of new cases of blindness in people over age 65.

-- Develop non-surgical methods to treat cataracts.

-- Improve methods of detection, diagnosis and treatment of glaucoma.

-- Identify the mechanisms responsible for the control of eye development and problems such as corneal diseases (dry eyes) and presbyopia (gradual loss of the eye's ability to change its focus from one viewing distance to another).

Nutrition. The U.S. Department of Agriculture Human Nutrition Center at Tufts University is conducting research to explore the relationship between nutrition and the maintenance of good health and to determine the nutritional and dietary requirements of the older population. Scientists are addressing three general areas of research which are of central importance to the center's mission: the nutrient requirements necessary to obtain optimal function and well-being for a maturing population; the role of nutrition in the development of major chronic, degenerative conditions associated with the aging processes; and the effects of nutrition on the progressive loss of tissue function with aging. Currently, the center is only about 70 percent filled, leaving many research opportunities unexplored.

This opportunity budget will allow the Center to pursue the following areas of research:

-- establish optimal diets in terms of fat and cholesterol content for the elderly to minimize cardiovascular risk factors and atherosclerosis.

-- investigate ways in which diet and nutritional status in combination with exercise and hormones (parathyroid hormone, vitamin D and estrogen) influence age-related loss of bone density -- osteoporosis.

Infectious Diseases. With age, the immune system becomes less efficient and is less able to fight certain infections. Many common infections, like the flu, can be particularly threatening to older people. The National Institute of Allergy and Infectious Diseases is involved in several projects to improve the ability of older people to fight-off infectious diseases:

-- Research at the University of Rochester Medical Center is investigating the effects of interferon, a substance produced by the immune system, on influenza in older people. The researchers concluded that interferon may prevent influenza in certain settings. Studies are needed to develop alternative methods of administering interferon and to determine the proper dose and duration of protection.

Research Resources. The Division of Research Resources of the National Institutes of Health funds general clinical research centers operating at major U.S. research medical centers. These centers comprise the majority of extramural patient research support.

Grantees from Boston's Beth Israel Hospital have found significant age-related changes in blood-pressure. Researchers discovered that aging increases the tendency for a person's blood pressure to fall sharply when standing up or after eating a meal, causing less blood to reach the brain. The result is an increase in fainting spells and falls among older people with a high risk of hip fractures, immobility, hospitalization and large health care costs. Further research is required to develop prevention strategies and treatments to offset the effects of common, everyday activities on blood pressure.

Dental Research. A recent survey by the National Institute of Dental Research found that 42 percent of adults age 65 and over were toothless. Those with teeth continue to suffer decay on both crowns and roots of teeth and often have severe and extensive periodontal disease problems. The causes and extent these problems remain largely unknown.

Epidemiologic studies to better identify the dental needs of older Americans and to understand how the oral environment changes with age can lead to an improved quality of life for many older Americans. We support the development of better preventive measures to make it easier for adults to maintain oral health. Funding to accommodate proposals for Research Centers on Oral Health in Aging announced by the National Institute of Dental Research last Fall should also be supported.

Diabetes. Diabetes is a disease in which the body does not produce or properly use insulin -- a hormone needed to regulate blood glucose levels. Over 11 million Americans have diabetes. One million of those have type I or insulin-dependent diabetes and nearly an estimated 10 million people have type II or non-insulin-dependent diabetes, which is generally age-related. Researchers are discovering that excessively high blood glucose levels in people with diabetes can lead to glycosylation of proteins, a process which protein cells become coated with glucose and eventually bind together. Gycosylated proteins may account, in part, for the development of some of the more severe complications of diabetes. Glycosylated proteins and the complications they cause also occur in a number of elderly patients. Scientists at the National Institute of Diabetes and Digestive and Kidney Diseases are now studying some of the links between diabetes and the aging processes.

Senator GRASSLEY. You stressed in your remarks that our major goal ought to be extending health-span, but not life span. How much debate is there about our ability to do just that? For example, would you say that there is a consensus among informed people around the idea that we will be able to shorten the period of incapacity at the end of life, as opposed to just extending life and thereby perhaps multiplying the total sum of incapacity among the old?

Mr. PERRY. Senator, at the conference at George Washington University which is taking place in connection with these hearings, there was testimony given just yesterday that shows that in the case of some of the chronic diseases, which I discussed earlier, your chances of having dementia, or osteoarthritis, or some of these other conditions double exponentially every 5 years after a mid-life, approximately 45 or 50.

So your chances of being hit with Alzheimer's disease at the age of 60 are only about 1 percent; but at 85 they are at about 30 percent. The risk doubles every 5 years. If we can simply postpone the onset of that doubling process, if we can shift that line 5 years closer to the end—because there is a finite life span—if we could shift it 5 years, that last doubling never takes place. It takes place beyond death, if you will. So we have effectively cut in half the incidents of dementia simply by postponing the onset of vulnerability by as little as 5 years. The same holds true for osteoarthritis, osteoporosis, and other conditions.

To answer your question, Senator, there certainly is a growing consensus in the scientific community that a fuller, more vigorous "health-span" of life can be lived very close to the end of life. In this scenario the period of time the true disability is compressed into a very short time. This is indeed a realistic and a hopeful possibility. It ought to be a national goal.

Senator GRASSLEY. Mr. Chairman, I have no further questions.

The CHAIRMAN. Thank you very much, Mr. Perry.

We are going to hear next from a panel on intervention in the aging process. The panel includes Allan Goldstein, Ph.D., professor and chairman of the George Washington University School of Medicine, Department of Biochemistry; Trudy Bush, Ph.D., assistant professor, Johns Hopkins University, School of Hygiene and Public Health, Department of Epidemiology; and Carl W. Cotman, Ph.D., professor at the University of California at Irvine, School of Medicine, Department of Psychobiology.

Will those witnesses please take seats at the witness table.

Mr. Goldstein, we would be delighted to have your testimony.

STATEMENT OF ALLAN L. GOLDSTEIN, PH.D., PROFESSOR AND CHAIRMAN, DEPARTMENT OF BIOCHEMISTRY, GEORGE WASHINGTON UNIVERSITY, WASHINGTON, DC

Mr. GOLDSTEIN. Thank you, Senator Melcher, Senator Grassley.

It is a pleasure to have the opportunity to address your committee to discuss the progress that has been made in research that offers the hope of significantly improving the quality of life of the elderly in the near future.

My area of expertise is as an educator and a basic research scientist. I am the co-discoverer, with the late Dr. Abraham White, of the thymosins, the family of hormones produced by the thymus which controls our immune system. I have been helping to direct the research efforts with these hormones from their discovery in 1965 to the present time.

It is a tragedy of life that we spend so many years trying to gain knowledge and wisdom. By the time we put it together, our bodies fall apart.

From my vantage point, there is absolutely no doubt that if major advances are to be made in improving the quality of life of the elderly, and in decreasing the staggering cost of the health care bill our country will be facing in the next 10 years, we must take strong and decisive action now to increase the priority for aging research within the Nation's science policy. We need to accelerate the pace and tempo of research now to capitalize upon the dramatic progress that has been made.

Scientists in the laboratories such as Dr.'s Makinodan, Doria, and Ershler, who will testify at these hearings, and others who are presenting their research findings this week at an international symposium at my medical center dealing specifically with biomedical advances in aging, are beginning to define the central reason for the downhill slide of health that begins in middle age. Much of it appears to hinge on the workings of the immune system. Such far-reaching advances have occurred in the field of immunology over the past 5 years, that it is now realistic to predict the emergence of potent new therapeutic agents which, by increasing the vigor of the immune system, will reverse and/or prevent many life-threatening diseases associated with aging.

Many of the key immunity hormones such as the biological response modifiers have been discovered. These hormones, such as the thymosins, interleukins, interferons, and other growth factors are being tested for the first time in humans with tremendous promise for success.

With the help of Nobel quality breakthroughs in biotechnology, such as in solid-phase peptide synthesis and in genetic engineering, we can now produce large enough quantities of these new medicines to treat diseases, whereas previously these substances could only be obtained in small amounts as they are found in trace amounts in the body.

These "new medicines" will also allow us to develop novel treatments to combat viruses, like the AIDS virus that does so much damage to the body's immune system and hopefully, will help reverse the age-related decline in immunity which increases the risk of pneumonia and other infectious diseases in the elderly, and which prevents people over the age of 65 years from being properly protected by vaccines that are effective in younger people.

In a few moments you will hear from Dr. Ershler and his colleagues that thymosin, one of these new medicines, appears to be useful in normal people over the age of 65 years to boost their immunity. Although we have an effective influenza vaccine, and have had one for several years, it does not work well in individuals who need it the most, namely the elderly and individuals who are immunosuppressed.

As a result, influenza remains a major cause of morbidity and mortality among the elderly, accounting for 20,000 to 25,000 deaths annually in the United States, despite immunization programs currently available. In addition, the substantial morbidity associated with influenza affects millions of elderly and costs health care providers hundreds of millions of dollars every year.

In the coming months, from human trials already in progress, and in some cases completed, it appears that new treatments will begin to emerge that hold the promise of significantly augmenting and/or in some cases replacing many of our old disease-fighting drugs. These "new medicines" will be less toxic because they augment the body's own immune system, rather than attempt to replace it, and are far more effective than anything medical science could possibly have predicted just a few years ago.

Indeed, the decade of the 1980's has ushered in a new age of scientific understanding which some have referred to as the "Age of Immunopharmacology." Through the thymosins and other biological response modifiers, we are beginning to learn how to manipulate and harness the energy of the body's immune system in the same way that we have learned to harness the energy of the atom.

Hopefully we will be able to rapidly translate these discoveries into the conquest of many diseases which are thought today to be incurable, and also provide new and safer medicines to treat and perhaps prevent some of the chronic diseases associated with the process of aging.

In the decade of the 1990's, if we plan carefully now, and if the Federal Government provides the mandate necessary to increase the progress and application of discoveries already made in biomedical research in aging, many of us in the scientific community believe we can help government to significantly decrease the staggering costs of health care for our senior citizens by increasing what Dan Perry has just referred to as, "our health span," that is, the number of years free from disease, decline and disability.

That concludes my testimony. I would be happy to answer questions.

[The prepared statement of Mr. Goldstein follows:]

UNITED STATES SENATE
SPECIAL COMMITTEE ON AGING
"Advances in Aging Research"
Wednesday, May 11, 1988

Allan L. Goldstein, Ph.D.
Professor and Chairman
Department of Biochemistry
George Washington University
Washington, D.C. 20037

INTERVENTION IN THE AGING PROCESS: Restoring Immune Function

Mr. Chairman and distinguished members of the Special Subcommittee on Aging, my name is Allan L. Goldstein. I am Professor and Chairman of the Department of Biochemistry at The George Washington University School of Medicine and Health Sciences in Washington, D.C..

It is a privilege to have the opportunity to address your committee to discuss the progress that has been made in research that offers the hope of significantly improving the quality of life of the elderly in the near future.

My area of expertise is as an educator and as a basic research scientist in the fields of biochemistry and immunology. I am the co-discoverer, with the late Dr. Abraham White, of the thymosins, the family of hormones produced by the thymus which controls our immune system, and have been helping to direct the research efforts with these hormones from their discovery in 1965 to the present time.

From my vantage point, there is absolutely no doubt that, if major advances are to be made in truly improving the quality of life of the elderly and in decreasing the staggering health care bill our country will be facing in the next 10 years (100 billion for caring for Alzheimer's patients alone), it will come about only by the government helping to accelerate the pace and tempo of biomedical research. That is the bad news! The good news is that dramatic progress in biomedical research in aging is being made!

Scientists in the laboratory such as Dr.'s Makinodan, Doria and Ershler, who will testify at these hearings and others who are presenting data this week at the International Symposium on, "Biomedical Advances in Aging, '88" at The George Washington University Medical Center, are beginning to define the central reason for the downhill slide of health that begins in middle age. Much of it hinges on the workings of the immune system. Such far-reaching medical advances have occurred in the field of immunology over the past five years that it is now realistic to predict the emergence of potent new therapeutic agents which by increasing the vigor of the immune system will reverse and/or prevent many life-threatening diseases associated with aging.

Many of the key immunity hormones and growth factors termed biological response modifiers (BRMs) have now been discovered. These BRMs, such as the thymosins, interleukins, interferons and other growth factors are being tested for the first time in humans with tremendous promise for success.

With the help of nobel quality breakthroughs in biotechnology, such as in solid-phase peptide synthesis and in genetic engineering, we can now produce large enough quantities of these "new medicines" to treat diseases, whereas previously

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these substances could only be obtained in small amounts, as they are found in trace amounts in the body.

These "new medicines" will also allow us to develop novel treatments to combat new deadly viruses, like the AIDS virus that does so much damage to the body's immune system and hopefully, will help reverse the age-related decline in immunity which increases the risk of pneumonia and other infectious diseases in the elderly and which prevents people above 65 years of age from being properly protected by vaccines that are effective in younger people.

The First Human Trials with Thymic Hormones

The first human trials with thymosin were carried out in the mid-1970's in children born with rare life-threatening immunodeficiency diseases. Because these children lacked a functioning thymus gland, they produced very few T-cells, the white blood cells needed for immunity, and usually, if they were not put in germ-free bubbles, died of overwhelmingly opportunistic infections within the first five years of life.

These early human studies established the safety and efficacy of thymosin in boosting immunity and provided the scientific rationale for further human studies with a man-made, synthetic hormone, termed thymosin α_1. Phase II and Phase III randomized trials underway include trials in patients with lung, head and neck cancer following radiotherapy, in immunosuppressed kidney dialysis patients, and in patients with infectious diseases.

In a few moments, you will hear from Dr. Ershler that thymosin may also be useful in normal people over the age of 65 years to help boost their immunity. Although we have had an effective influenza vaccine for several years, it does not work well in individuals over the age of 65 or in immunosuppressed individuals. As a result, influenza remains a major cause of morbidity and mortality among the elderly, accounting for 20,000 - 25,000 deaths annually in the United States despite the immunization programs currently available. In addition, the substantial morbidity associated with influenza affects millions of elderly persons and costs health care providers hundreds of millions of dollars every year. Similar to Dr. Ershler's studies, Dr. Steve Shen and his colleagues at the University of Maryland Medical Center will be reporting this week at our meeting that they have found that they can significantly boost response rates in kidney dialysis patients and increase antibody titers to both the influenza vaccine and the hepatitis vaccine by giving thymosin α_1 with the vaccine. Of key importance, Dr. Shen has found that the ability to increase antibody titers to influenza is age-dependent. Dialysis patients, in fact, may represent a good model to study accelerated aging of the immune system. Of interest is the observation that the older the patient, the greater the degree of immunosuppression and the greater the response rate with thymosin.

It is clear from these studies and others in progress that in the future thymosin and its relatives may become to disorders of the immune system what antibiotics are to bacterial diseases today: a ready arsenal of highly specific weapons for maintaining health and increasing the quality of life. These examples of the far-reaching advances that have occurred over the past five years made it possible for us to begin to understand how the immune system works. With this knowledge, which has come primarily from the lab bench, we have begun the process of technology transfer and are developing new and powerful weapons to fight disease.

To summarize my testimony, in the coming months, from human trials already in progress and, in some cases completed, it appears that new treatments will begin to emerge that hold the promise of significantly augmenting and/or in some cases replacing many of our old disease-fighting drugs. These "new medicines" will be less toxic because they augment the body's own immune system rather than attempt to replace it and are far more effective than anything medical science could have possibly imagined just a few years ago.

Indeed, the decade of the 1980's has ushered in a new age of scientific understanding which should properly be called the "Age of Immunopharmacology". Through the thymosins and other biological response modifiers, we are beginning to learn how to manipulate and harness the energy of the body's immune system in the same way that we have learned to harness the energy of the atom.

Hopefully in the decade of the 1990's, if we plan carefully now and if the federal government makes the funding commitments necessary to complete the job, we will be able to rapidly translate these discoveries into the conquest of many diseases which are thought today to be "incurable" and also provide new and safer medicines to treat and perhaps prevent some of the chronic diseases associated with the process of aging.

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The CHAIRMAN. Thank you, Doctor. I believe we will hear from the other two members of the panel and then we will have some questions.

Ms. Bush.

STATEMENT OF TRUDY L. BUSH, PH.D., M.H.S., ASSISTANT PROFESSOR, THE JOHNS HOPKINS UNIVERSITY, SCHOOL OF HYGIENE, AND PUBLIC HEALTH, DEPARTMENT OF EPIDEMIOLOGY, BALTIMORE, MD

Ms. BUSH. Thank you very much. Good morning. Thank you for the opportunity to present my testimony today.

My name is Trudy Bush and I am an Assistant Professor of epidemiology at Johns Hopkins University.

Two of the major health problems in older women in this country are cardiovascular diseases and osteoporosis. Both of these conditions are major causes of disability and death in American women, and theoretically, both can be delayed or prevented entirely. However, more information is needed in order to develop successful ways to delay or prevent the occurrence of both cardiovascular disease and osteoporosis in older women.

I think it is not a well-known fact that in the United States, cardiovascular disease is the leading cause of death for women. Two out of every three women over the age of 50 years will die from cardiovascular disease. In 1984, nearly 500,000 American women died from cardiovascular diseases. This is nearly 2.5 times the number of women that died from breast cancer, lung cancer, colon cancer, ovarian cancer, accidents, influenza, pneumonia, liver disease, and diabetes combined.

Cardiovascular diseases are also the leading cause of serious disability among older women. It is estimated that over 3 million to 6 million American women are now disabled and unable to carry out their usual activities because of cardiovascular disease. The cost of this condition in women is estimated to be over $9 billion annually.

Despite the magnitude and seriousness of cardiovascular disease in women, little information is available about the causes of this condition. This lack of information reflects the fact that cardiovascular disease occurs two to five times more often in men than in women, and most studies and clinical trials to date have focused primarily or exclusively on men. I just would like to remind the committee that two-thirds of all older people are women.

There is now data from several epidemiologic studies which suggest that the risk of cardiovascular disease in older American women can be reduced 40 to 60 percent by the use of estrogen therapy. Additional research into the safety and effectiveness of estrogen therapy is needed and preliminary studies are now underway. If a hormonal regimen prove to be both safe and effective, this therapy could radically alter the mortality and morbidity experience of American women.

Osteoporosis, or a loss of bone mass predisposing to fracture, is also a very important public health problem for older American women. One out of every four American women over the age of 60 is affected by osteoporosis. Each year there are 200,000 hip fractures resulting from osteoporosis. The consequences of hip frac-

tures are severe. Risk of death, risk of institutionalization, and risk of permanent disability and dependency are greatly increased in women who suffer a hip fracture. Medical costs associated with these hip fractures have been estimated to be $7 to $10 billion annually.

Estrogen therapy after the menopause has also been shown to be highly effective in preventing both bone loss and hip fracture in older women. However, currently only about 10 percent of American women use hormonal therapy and usually this is short-term treatment of menopausal symptoms.

In summary, the public health problem with cardiovascular disease and osteoporosis in older women will continue well into the next century. It is projected that 30 years from today, in 2020, there will be over 30 million American women over the age of 65. These women will be at significant risk of both death and disability from cardiovascular disease and osteoporosis. Further research is needed into the causes and preventions of these conditions.

Thank you. That ends my testimony.

The CHAIRMAN. Thank you Dr. Bush.

Dr. Cotman.

STATEMENT OF CARL W. COTMAN, PH.D., PROFESSOR, UNIVERSITY OF CALIFORNIA, IRVINE, SCHOOL OF MEDICINE, DEPARTMENT OF PSYCHOBIOLOGY, IRVINE, CA

Mr. COTMAN. Thank you very much, Senator.

I would like to comment on the aged brain and its resilience and self-repairing capacity.

Most people even today, still hold to the idea that once development is ended, the brain's growth and restoration capacity are really gone. Statements like this were developed by Ramon y Cajal who said that, "In adult centers, the nerve paths are something fixed, ended, immutable."

However, today it has become clear that the aged brain has the capacity to rewire its damaged circuitry. The stimulus may be a perturbation such as trauma, a metabolic insult, or even a degenerative disease such as Alzheimer's disease. The healthy cells that remain have the capacity to grow and replace damaged circuitry.

It is much like thinking of the brain as a computer. But this is a very special type of computer. It has the capacity to repair itself. We can learn much from these processes, how we can intervene, and perhaps even develop some new concepts on brain function of use to high technology.

Recently, it has been shown by my group and others that neuronal regrowth even occurs in the course of Alzheimer's disease. Normally we think of Alzheimer's disease as being degenerative with no reserve capacity in the brain cells. But the capacity, even in Alzheimer's disease to regenerate, indicates a vital reserve capacity, and points to a research area which can be tapped for therapeutic intervention.

Now I would like to discuss progress in the area of molecular and cell biology of brain function in the aged.

Recently we and others have been studying a class of molecules called nerve growth factors, or neurotrophic factors. These mole-

cules have the capacity to act on old neurons that are shrunken and make them expand again. These molecules can also stop neurons in the aged brain that have been traumatized from dying.

We recently reported on a particular new growth factor called fibroblast growth factor. There are several of these. My own belief, and I think that of others, is that this is an exciting new research area which opens up a new level of therapeutic intervention into the aged nervous system.

What is it that controls these factors? How can we stimulate their production? How can we manage to get them into the brain? Unfortunately, they're large molecules, so in animal studies, they have been infused directly into the brain. But the results are astonishing. Even animals with behavioral deficits in elderly can be restored by the infusion of these factors.

I think what we are seeing here is the beginning of a major new thrust in research that is refuting the old dogma that the brain does not have resilience and a reserve capacity. Indeed, it is this capacity to keep repairing and updating its circuitries that probably gives us better brain function through life.

I would like to close with a quote or prophesy from the very person who first started the dogma that the brain couldn't regrow, that its circuits are fixed, immutable. "It is for the science of the future to change, if possible, the harsh decree. Inspired with high ideals that must work to impede or moderate the gradual decay of neurons to overcome the almost invincible rigidity of their connections, and to re-establish the neurofunction when disease has severed centers that are intimately associated." Ramon y Cajal, 1928.

Indeed, we are within reach of this goal armed with the new technology and the minds and the talents of this country.

Thank you.

[The prepared statement of Mr. Cotman follows:]

United States Senate
Special Committee on Aging
"Advances in Aging Research"
Wednesday, May 11, 1988

Carl W. Cotman, Ph.D.
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University of California at Irvine
Irvine, California

THE AGED BRAIN: ITS RESILIENCE AND SELF-REPAIRING CAPACITY

For years, it was believed that the central nervous system was incapable of growth or repair processes. This view was summarized by Cajal and was dogma for over three decades.

"*But the functional specialization of the brain imposed on the neurons two great lacunae: proliferative inability and irreversibility of intraprotoplasmic differentiation. It is for this reason that, once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centers the nerve paths are something fixed, ended, immutable. Everything may die, nothing may regenerate.*" S. Ramon y Cajal, '28.

However, in the last several years it has become clear that this is not true. With the proper stimulus the brain has the capacity to rewire its damaged circuitry (e.g., synaptic plasticity). Even the aged brain has this capacity. The stimulus may be a perturbation such as trauma, or a metabolic insult, or it may be more subtle, such as a modification in behavior or learning a new task. The stimulus may also be a graft ("transplant") of neural tissue or a chemical (e.g., neurotrophic factor). Nearly whole neuronal networks can be replaced by implanting fetal neurons into adult brain. The brain in its wisdom has a program to repair itself from its minor injuries. It is self-repairing.

The observation of neural regeneration will help us to understand and develop strategies to treat the changes that occur in the aged human central nervous system. Reactive growth can maintain function if a portion of the circuit remains intact. As cells are lost, new connections are made by the remaining healthy cells that assume similar functions of the fibers from the same or converging pathways and may amplify weakened signals. This maintains functional stability despite the cell loss. The remaining cells assume more of a workload in order to keep the connections at their normal levels.

Neuronal regrowth also appears to occur in Alzheimer's Disease (AD), a disease previously thought to be degenerative with no reserve capacity in the brain cells. Generally, disease-induced neuronal loss in the AD brain acts as a stimulus in a manner similar to that of specific lesions in the rat brain. For example, the selective loss of cortical neurons removes the input to a critical memory structure, inducing a compensatory response from adjacent neurons. The observed expansion of a work load and the increase in the activity of various neurons are in marked contrast to the numerous reports of reductions in transmitter-related parameters in Alzheimer's disease. Compensatory growth in the course of a degenerative disease indicates that the resultant circuitry cannot be simply considered as a loss in neural elements. In AD the brain is also self-repairing, at least to a degree. However, in disease, some of the compensatory changes may ultimately become part of, and actually contribute to pathology. The capacity of the aged and AD brain to regenerate indicates a vital research area exists which can be tapped for therapeutic intervention.

As these exciting new concepts were developing another more subtle revolution was occurring in the area of aging research. It is generally believed that behavioral functions such as cognition, learning and memory decline with age, a consequence of the price of growing old and losing brain cells. Yet in current studies, many key parameters do not show age related declinesin both animals and man. In man it was recognized that some individuals clearly age more successfully than others. In fact, some functions increase; artistic ability, statesmanship,and wisdom, for example.

We now understand that some age related losses are not inherent to aging at all. They are caused by prolonged stress, early insult and disease. The notion that the brain has resilience and can even repair itself is indeed exciting. It provides data to support the hope that functional decline is not inevitable.

Molecular biology in its own right is making the third contribution to this triangle of innovation. Every field depends on its technical "tour de force". I would like to illustrate one such example, again from my own work at Irvine. We and others have identified a class of special proteins made by the brain that are entrusted with maintaining neurons, stimulating their growth and protecting them from insults. These molecules are called growth factors, or more properly, neurotrophic factors. In the aged human brain, some neurons die while others shrink with age. We recently reported in *Nature* that a particular molecular factor (FGF) will reverse this process in the aged brain.if applied to the neurons.

These and selected data on another factor , NGF, offer great hope for the future. What increases the output of these? We showed recently that injury itself will probably act as part of the self repairing design. What are the other natural regulators. Do some individuals maintain these factors better than others? Does environment and stress change them?

The central nervous system detects signals from the environment, and from within the body, and sends out signals that elicit proper responses. Unlike other tissues, brain cells operate in highly integrated networks. The total output must be meaningful, purposeful and ultimately adaptive in response to an ever changing environment. As described in my full report, the nervous system can compensate for some losses due to aging.

Current neuroscience research is making great strides in discovering the mechanisms that underlie aging and in finding means to enhance circuit function when it is compromised. Indeed, this was in fact , predicted.

"It is for the science of the future to change, if possible, this harsh decree. Inspired with high ideals it must work to impede or moderate the gradual decay of the neurons, to overcome the almost invincible rigidity of their connections, and to re-establish normal nerve paths, when disease has severed centers that were intimately associated." S. Ramon y Cajal., '28.

We now have an unprecedented opportunity to understand and build on the brain's own repair plan. We have the ability to improve the quality of life for longer in the aged.

The CHAIRMAN. Thank you, Dr. Cotman. Earlier I said, what could be coming on in research that would assure the elderly that you could still enjoy life at 80. I can't think of anything more monumental than the research you're involved with if it is true that you can repair worn out circuitries or diminished circuitries of the brain. That would be the most reassuring thing, for the elderly that we could conceive.

What are the possibilities of your research? You mentioned neuron repair. Is that correct?

Mr. COTMAN. Yes. I mentioned neuron growth factors that stimulate neuron repair and improve function. Some of them occur naturally in the brain.

The brain has the capacity to sprout and grow again, which is something that means there is a natural molecular mechanism for it. As we learn about these mechanisms and how to control these growth factors, my belief is that we will be able to give more resilience to the brain, even impart a resistance to insults like toxins, small strokes, and so on. Those factors are not only repairing the brain, but they're kind of little guards protecting it against various insults.

Unfortunately, there's not enough basic research being done on these. We believe there are more growth factors that haven't been discovered yet. This requires some fairly dedicated research teams with long-term stability because it is not an easy job. They are present in very low concentrations. Ultimately they offer great hope.

The CHAIRMAN. Dr. Goldstein, thymosin is a naturally occurring hormone?

Mr. GOLDSTEIN. Yes. It is actually a family of hormones, small peptides, that were first isolated from the thymus gland and are now produced chemically by solid phase peptide synthesis.

Initial clinical studies in the 1980's were directed toward this group of children with very rare diseases, but now most recently, thanks to several clinical studies that have been carried out that you will be hearing about this morning, we are now applying that same information to treat the other end of the life span.

As we age, one of the very first things to occur is that the thymus gland begins to shrink. It actually begins before the onset of puberty. With that decline in thymic size, comes a decline in function of the thymus, which functions as the master gland of the immune system. As fewer of these biologically active hormones are able to circulate in the body, we lose some of our immunity and resistance to disease. That's one of the major reasons why the elderly, we believe, are highly susceptible, to infectious diseases, and why effective vaccines such as the influenza vaccine, do not work very well in this older group because of their decline in immunity.

We have now been able to translate those findings in children to the elderly with, I believe, great promise for success in the not too distant future.

The CHAIRMAN. In other words, does that follow that perhaps I have a better level of thymosin?

Mr. GOLDSTEIN. Well, yes and no. The fact that every year there may be new strains of influenza appearing would necessitate a new series of vaccinations in order to maintain your immunity against

that new strain. In young people, that is in individuals less than 65 years of age, the typical influenza vaccine is effective in perhaps 75 percent of all individuals vaccinated in protecting them from influenza.

However, in the elderly, because they have lower levels of thymic hormones and, therefore lower levels of immunity, the vaccine only protects about 25 percent of these individuals. There are genetic factors involved in why that 25 percent of the population is protected, but not the other 75 percent.

The CHAIRMAN. And thymosin is a factor?

Mr. GOLDSTEIN. Right. By giving thymosin back to these elderly individuals, from studies you will hear about this morning, you can boost the 25 percent effectiveness of the vaccine up to about 75 percent. You can make a vaccine more effective in the elderly.

The CHAIRMAN. Dr. Bush, estrogen is a naturally occurring hormone. That has something to do with preventing osteoporosis. Is that correct?

Ms. BUSH. Right, both osteoporosis and cardiovascular diseases.

The CHAIRMAN. Are there other steps that women can take to help guard against heart disease and osteoporosis?

Ms. BUSH. There are hygienic methods, such as moderate exercise, and moderate dietary restrictions on fats. But in terms of actually having a substantial beneficial effect on bone loss and heart disease, estrogen therapy far outweighs any of these hygienic therapies.

For example, with bone loss and estrogen use, if one increases calcium intake, you may decrease the loss of bone by 1 percent a year. With estrogen therapy, you'll decrease it 70 percent.

The CHAIRMAN. Dr. Goldstein, I don't quite understand this. Is thymosin used now in therapy?

Mr. GOLDSTEIN. Thymosin is now in phase 2-3 clinical trials and, as an adjuvant with influenza in the elderly, it is actually in phase 3 trials, the last stage in clinical testing. We are hopeful that thymosin alpha one, the synthetic hormone being tested, will be the first of the biological response modifiers to be approved for major applications in the elderly.

The CHAIRMAN. We can expect a conclusion say in the next 2 years?

Mr. GOLDSTEIN. Perhaps even before then. There is a major trial, the largest study ever conducted in the United States or the world with thymosin alpha one, that has just been completed here in Washington at the U.S. Soldiers' and Airmen's Home. The data is being analyzed now. Hopefully, within the next 4 to 6 weeks, it will be available.

If those studies confirm the trials that you will be hearing about from Dr. Ershler's group at the University of Wisconsin, it is hoped that the results will accelerate that timetable, so that within 2 years we will be able to apply this new approach to hopefully lowering the incidence of influenza and pneumonia in the elderly.

The CHAIRMAN. Thank you. Thank you, very much. Senator Grassley.

Senator GRASSLEY. Mr. Chairman, I want to bring up with Dr. Bush the point you brought up. As I recall, in your testimony you said that only about 10 percent of women make use of estrogen

therapy because of problems that it has for some. What are those safety considerations that are a problem so we don't have greater use of it?

Ms. BUSH. Right. Unopposed estrogen therapy in women with a uterus has been shown to increase the risk of uterine cancer. Women who take estrogen therapy probably have between two and eight times greater risk of developing uterine cancer than women who don't. So that is primarily the major contraindication for unopposed estrogen therapy right now.

Estrogen in high doses has been shown to increase the risk of thrombophlebitis and thromboembolism, but in the doses usually used for menopausal woman, this doesn't seem to have been a problem.

I might point out, Senator, there is data that shows women who take estrogen therapy and develop endometrial cancer probably from the estrogen therapy, actually live longer than women who don't take the therapy at all because it is a highly curable cancer and is usually found because they are on therapy and they are being followed. It is usually found at a very early state.

Senator GRASSLEY. Is there any research going on that would indicate solutions to some of these problems? I know cancer research has been going on for a long time, but does it look like there's hope of overcoming some of these problems so there will be greater use of this type of therapy?

Ms. BUSH. There's currently a clinical trial underway. We are about ready to start recruiting patients this summer. It's called post-menopausal estrogen and progestin intervention, or PEPI for short.

The purpose of this trial is essentially to find the most effective and the most safe estrogen or hormonal replacement therapy for menopausal women. I think within the next 3 years—the trial is scheduled to go 3 years—we should have very good data on the most effective and safe hormonal replacement therapy for menopausal women.

Senator GRASSLEY. Thank you, Dr. Bush.

The CHAIRMAN. Senator Domenici.

STATEMENT BY SENATOR PETE DOMENICI

Senator DOMENICI. Mr. Chairman, first let me apologize for being late. If you will permit me to, I would like to make a very brief statement in observation.

The CHAIRMAN. Certainly.

Senator DOMENICI. I would have asked Dr. Dan Perry, who I understand gave an early overview of the Alliance for Aging Research and the National position. I want to complement them on their approach.

Obviously, this committee and many committees in the Congress, struggle mightily regarding the costs of health care and the current problems people have, in particular some difficulties in the Medicare area of delivering health care to the seniors. I think it is exciting that a group of senior citizen advocates would be talking about the fact that while we're busy handling those kind of costs, and those kinds of problems, that we ought to focus mightily on

prevention and cures and scientific interventions of which we are not currently aware.

I also think, to concentrate at this time and urge that the National Institute on Aging focus on Alzheimer's is a rather appropriate establishment of a priority.

I also understand that Dr. Dan Perry, representing the Alliance for the Aging Research, is a supporter of a major new American initiative which is just beginning to reach national attention. That is, the mapping of the human genome. That is a very strange word. When I talk about it, people ask what in the world is the genome. I am learning from you all to at least try to explain it.

Essentially, as I understand it, we know that at least 3,000 diseases and/or ailments have some link to our genetic makeup. As I understand it, if we proceed to map the human genome, what we really will be doing is mapping the basic building block of human life, that is, the blueprints of the human body, if you will—a very monumental job. We have been doing it in a cottage industry manner. That is not said pejoratively.

Scientists have been picking one genetic ailment and researching it. We are now finally getting to the point, between the National Institutes, the medical professional, the Department of Energy, the President's science advisors, where they are finally telling us we ought to pool together and have a national policy to proceed with the mapping of the human genome.

I urge that the senior groups that are worried and concerned about the future, look carefully at two thrusts here in the U.S. Senate: One is Senate bill 1966, Mr. Chairman, which is a proposal called the Biotechnology Competitiveness Act; the other is Senate bill 1480. Both of those would create a National advisory panel to set in motion a multi-year program for the evolution of the mapping of the human genome in both developing better the scientific pools to do it, and then telling the country how quick we ought to do it—10 years, 5 years, 20 years. It is estimated, Mr. Chairman, that if we proceed as we are, it will take about 100 years because we are just picking around the edges.

Maybe, if we focused on it, we could do it in 10 to 15 at a national cost of somewhere $200 and $300 million, between the National Institutes of Health and the Department of Energy, which has developed the gene bank and some of the equipment.

This won't cure anything as I understand it, Dr. Goldstein, will it? This mapping will be a diagnostic capability that we will hand over to the scientists of America and the world for them, as I understand it, to dramatically enhance and focus their scientific research because we will know the relationships of the mapped and somewhat sequenced genetic system of the human body.

I frankly understand that we are not alone in this quest for a scientific breakthrough. The Japanese are busy working on it. I don't think we ought to necessarily, when it comes to health, be worried about the fact that they are. We probably ought to be glad they are because wellness and cures and health are wellness and cures and health.

I think it does have a dramatic impact on our future in terms of being the world leader in medicine, diagnostic equipment, pharma-

ceuticals and in a very real sense, the world's leader in wellness and health.

Having said that, that is much more that I should be saying here, but could I please take a risk, not having talked to you and asked you if you would share with committee whether you generally, or otherwise, support a major American effort at mapping the human genome? Could we start with you, Dr. Goldstein?

Mr. GOLDSTEIN. I think basically the view of the scientific community is that all disciplines of biomedicine will benefit tremendously once we have the basic information that determines the genetics of living things—the complete human genome.

From my point of view, it should be a major goal. There is widespread support for this endeavor. It will help, not only American science, but world science as well. I would like to point out to you that, and I know your committee is certainly aware of this, many of the outstanding scientists in Japan and in Europe around the world who are already working on various phases of this project now, were trained by the professors and scientists in the United States.

With the leadership we have shown in the past in science, we have been able to get to this point. I think this would be an opportunity to provide new, fresh leadership in a very important area of science. I hope your efforts to secure funding for the entire mapping are successful.

Senator DOMENICI. Dr. Bush?

Ms. BUSH. I concur with Dr. Goldstein.

Mr. COTMAN. Certainly it is one of the exciting new frontiers. To really have the dictionary available would perhaps help us understand why it is that some people age more successfully than others. There are really many mysteries in the area of aging that have to ultimately go back to the gene level.

It is not to say that everything is going to be just straight genetics; there are obviously clear environmental components. I think that this program is important, particularly if it is associated with the development of technology to go with it so that we are ready to use that dictionary when it becomes available. The program will then be really lauded by the scientific community.

Senator DOMENICI. Mr. Chairman, I don't do this very often, but I want to urge consideration of these two bills, or at least one of them. One is very limited. It sets up the national panel for the first time with the Director of the National Institutes of Health and the Secretary of Energy as co-chairmen, rotating. They are charged with introducing an American game plan and telling the Congress and the President how we ought to implement it and who ought to be doing it.

The other is a more specific bill in that it assigns some duties. We have struggled through, as you might suspect, some competition between institutions. I think we are over that now. The National Institutes of Health clearly has a prerogative and a role, and they were concerned about interfering with current, specific work. The Department of Energy, quite by accident has the technology for the mapping and the gene bank because of their having been charged to do the research on the genetic aspects of nuclear activities. They happen to be out front.

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I think we have resolved those differences and I would certainly urge, if you and the committee have time, that you consider an early evaluation and maybe we can urge the Aging Committee to support the efforts of the Labor, Health and Human Resources Committee and the Energy Committee in trying to move this along.

I don't think there is any question that the senior citizens here and in the world would probably stand in the long run to benefit more if we had the entire genome system mapped, as the doctor said, in a way that is deliverable to the scientific community so that the various conclusions can be drawn from this new dictionary of relationships.

It is just a giant tool to set you on the right path of research, as I understand it. You might otherwise be researching around the edges for 30 years, whereas this might get you right to the issue. It might find numerable cures; as I understand it, we've only succeeded in a couple of cures for genetic diseases. Is that not right, doctor, in the all so many years we have researched?

Mr. GOLDSTEIN. That's true. There are a number we are very close with, but this certainly would just open up new horizons and increase our understanding of many, many genetic diseases.

Senator DOMENICI. Thank you very much, Mr. Chairman.

The CHAIRMAN. Thank you Senator Domenici for elaborating on those two bills. This committee will be delighted to assist in pushing along the recognition of the necessity of one or the other. Of the two, which is the preferred bill?

Senator DOMENICI. Frankly, Mr. Chairman, we've got the Labor, Health and Human Services bill which I co-sponsored with Senators Chiles and Kennedy. It got rid of the conflicts between the institutions and set up the national panel to establish goals, but it doesn't do anything more. So if we did that, that would be one giant step.

The Energy Committee bill, which is essentially 3 years of effort on my part with three or four Senators, has a more difficult time because it is a little more specific in terms of who ought to do what. It also establishes a much broader framework for using the national laboratories more effectively with the private community of the country. So, that takes a little longer to get through.

I think either would do the job. The former would probably have a better chance of getting through here and in the House quicker.

The CHAIRMAN. Thank you very much and I commend you for your efforts on this.

I want to thank the members of this panel for your fine testimony. I wish you Godspeed in your work.

Our next panel consists of Dr. David Kritchevsky, Associate Director for the Wistar Institute of Anatomy and Biology in Philadelphia; and George G. Glenner, M.D., Professor, University of California, San Diego, School of Medicine, Department of Pathology, La Jolla, California.

Please take your seats, gentlemen. We will hear first from Dr. Kritchevsky.

STATEMENT OF DAVID KRITCHEVSKY, ASSOCIATE DIRECTOR, WISTAR INSTITUTE OF ANATOMY AND BIOLOGY, PHILADELPHIA, PA

Mr. KRITCHEVSKY. Thank you Senator Melcher. I am grateful for the opportunity to address this committee.

My name is David Kritchevsky. I am the associate director of the Wistar Institute in Philadelphia, which is the oldest independent biological research institute in the country. I am also professor of biochemistry at the University of Pennsylvania in both the Schools of Medicine and Veterinary Medicine.

I would like to read a brief general statement and follow it with a few comments on some of the more exciting current research.

The mandatory first step in addressing the nutritional needs of the elderly is the establishment of a data base from which we can draw conclusions as to requirements, prescribe treatment and predict outcome. The bulk of existing information is an extrapolation from data relating to younger adults.

Physiological changes in aging include changes in taste and smell, which affect eating behavior, changes in digestion and absorption of food, and dental problems which limit accessibility to food. Elderly subjects absorb simple sugars less efficiently than younger ones; their ability to absorb protein and fat is also reduced. In the face of these diminutions in function, the data suggest that the caloric intake may be generally lower than recommended so that available levels of iron and other important micronutrients are reduced.

Furthermore, the environment of the elderly may be an institution or they may live independently. Each setting presents its own set of problems and requirements.

The foregoing generalizations which can be made about the factors impinging upon nutrition of the elderly are compounded by consideration of specific disease states which are accentuated in old age. Chronic digestive disease, for instance, shows dramatic increases when subjects age 45 and over are compared to subjects age 65. For instance, there is a 27-fold increase in diverticular disease, a 4-fold increase in constipation and increases in colitis, gallbladder disorders and other diseases. Each condition brings with it specific requirements for treatment.

We have to combine investigations of general health among the elderly with information on their status regarding specific micronutrients, such as iron, copper and selenium, and vitamins. The task becomes more difficult because the various nutritional indices are affected by economic status, ethnicity and geographical location. It may be that we will have to develop a series of nutritional assessments and treatments rather than one simple recipe. Basically we need a definition of "normal."

The data suggest the need for foods of high caloric density which appeal to the eye and palate, and are easy to prepare and inexpensive. Nutritional assessment will permit us to provide prescriptions which can fill the requirements for the healthy elderly and speak to the needs of the specific age-related deficiencies. As others have already told you, we cannot guarantee prolonged life, but we can aim at easing the vicissitudes of aging.

For the healthy, the best recommendation may be that given by Dr. Elsie Widdowson, a world famous British nutritionist who, in her 80's is still vigorously engaged in research programs on both sides of the Atlantic. Dr. Widdowson says, "My recipe for nutrition in extreme old age is well fitting dentures, portions of ordinary meals, milk to drink with all of them and anything the individual particularly fancies, whether it be fish, fruit, cake, or chocolate." I would add tender loving care.

Having said this in generalization, I think that what is very exciting currently is data which show that caloric restriction—and by that I mean that the subjects, or the animals being used get all of everything they need, just less of it—prolongs life in experimental animals, even when commenced after—for instance in mice, when they've reached half their life span. Caloric restriction in rodents has been shown to inhibit tumor promotion and tumorigenesis in general, whether the tumor be related to a chemical, x ray, or radiation or is spontaneous, such as a virus. That ends my testimony.

The CHAIRMAN. Thank you, Doctor.

Dr. Glenner.

STATEMENT OF GEORGE G. GLENNER, M.D., PROFESSOR, UNIVERSITY OF CALIFORNIA, SAN DIEGO, SCHOOL OF MEDICINE, DEPARTMENT OF PATHOLOGY, LA JOLLA, CA

Dr. GLENNER. Senator Melcher, committee members, my name is Dr. George Glenner and I am a Research Professor of Pathology at the University of California, San Diego, School of Medicine. I am also the Chairman of the California State Task Force on Alzheimer's disease.

The number of people with Alzheimer's disease is expected to triple within the next 15 years. The direct cost to families and taxpayers to care for the 2.5 million victims, as you have heard, is presently estimated over $48 billion. This is more than the total cost for care of heart disease, cancer, and stroke combined, the three leading causes of death in the United States.

If we do not find the cause and cure of Alzheimer's disease, the direct cost for caring for its victims by the year 2000 will be over $144 billion. The impersonal economic facts are that Alzheimer's disease alone, could grease this country's slide into bankruptcy. If nothing else, these facts by themselves, should set the biomedical research priorities for our Federal Government.

I will now tell you of the discovery of the silk fiber protein of Alzheimer's disease. Since Alzheimer's disease is not caused by aging, yet, much like diabetes and many other disease processes, increases in incidence with advancing age, we describe it as age-related. Our specific study of Alzheimer's disease began in my laboratory in 1979 at the National Institutes of Health. Although the lesions of the senile plaque and neurofibrillary tangles—this is a picture I hope you can see, but the audience unfortunately can't—of the tangles of Alzheimer's disease in which the nerve cell is replaced by silk fibers. A plaque which is outside the cell is also made of silk fibers right here and this destroys tissue outside of nerve cells. Here is another picture of a tangle here. Here are the plaques and the tangles that Alzheimer originally described.

In our studies, we obviously saw the hallmarks of the disease which Dr. Alois Alzheimer described. We were able to show that there was another lesion involving the blood vessels in the brain that was an almost invariable accompaniment of the disease. Here you can see the silk fibers in the walls of the blood vessels. The bright color represents the presence of silk fibers which have been given the name, "amyloid." These are the amyloid fibers of Alzheimer's disease.

Senator DOMENICI. Mr. Chairman, may I ask a question?

The CHAIRMAN. Certainly.

Senator DOMENICI. What diagnostic tools gave you those results?

Dr. GLENNER. We used a polarizing microscope on specially stained tissue. What you're looking at is a polarization color as a result of using a very sophisticated microscope.

Senator DOMENICI. Have you concluded that is symptomatic solely of Alzheimer's?

Dr. GLENNER. We say these three lesions together are symptomatic, as you say, of Alzheimer's disease. So, if you saw this in a tissue section, you'd be able to say this patient had Alzheimer's.

Senator DOMENICI. Thank you, Mr. Chairman.

Dr. GLENNER. This involvement by the blood vessels caused by the silk fibers, or amyloid, was a significant added bit of information.

When our laboratory moved to the University of California, San Diego in 1980, we sought to isolate the silk fibers of the brain's blood vessels in Alzheimer's disease in order to analyze them chemically and, thus, possibly to determine their origin and cause.

In 1984, our laboratory isolated the amyloid material that you see in these pictures from blood vessels and determined the sequence of the amino acids, or building blocks, of the protein. A computer search revealed this to be a new protein, never previously described. We designated it as the "beta protein." This protein not only was found in the blood vessels as part of the amyloid, or silk fibers, of the blood vessels. It was also found in the plaque as part of the plaque material. Later it was found to be a component of the tangles. So, all three lesions of Alzheimer's disease appear to have this particular protein as a major component.

Plaques and tangles and deposits of amyloid in cerebral vessels occur also in individuals over 40 years of age having Down's Syndrome, which is the most common cause of mental deficiency in children and thought to be the result of an extra copy of chromosome 21.

We also decided to try to isolate the silk fibers from blood vessels in aged Down's individuals who had died. At autopsy, we isolated the amyloid-laden vessels and we found that the protein that made up the silk fibers in both Alzheimer's disease and Down's Syndrome was essentially identical.

This finding irrevocably linked Alzheimer's disease to Down's Syndrome. We, therefore, predicted that the gene coding for this protein would reside on chromosome 21, which is the abnormal chromosome in Down's. Therefore, Down's Syndrome would now become the first predictable model for Alzheimer's disease.

What that means, simply, is that we can never predict just by walking around the room, who will eventually acquire Alzheimer's

disease. But most of us are capable of recognizing most Down's individuals. We know they will, by the time they get to be 40, all come down with the same lesions as will Alzheimer's individuals, that is, they are a predictable model.

Indeed, within 4 years, three groups independently identified the amyloid protein to be on chromosome 21, so it was a marker for the disease. This gene codes for a larger protein—the beta protein which is in the silk fibers is a small segment of it. When improperly digested, that is by an abnormal enzyme, a small portion of the larger parent protein molecule forms amyloid silk fibers in the substance, the vessels and the nerve cells of the brain.

These later studies, which were supported by a research grant from the National Institute on Aging, strongly suggests that there exists an abnormal gene coding for an enzyme which is defective and causes improper cleavage of the larger beta protein to produce the smaller protein that forms the silk fibers. If such a theory is proven correct by the finding of a defect in an enzyme digesting the large protein, then therapeutic approaches to Alzheimer's should readily follow, for example, by inactivation of this enzyme, as should approaches for definitive diagnostic tests for Alzheimer's disease, which do not presently exist.

We are very optimistic that if research funding increases, within the foreseeable future, both a diagnostic test and a treatment for Alzheimer's disease will be found.

Thank you very much. That ends my testimony.

[The prepared statement of Dr. Glenner follows:]

George G. Glenner, M.D.

Testimony For
The Senate Special Committee on Aging

Hearing, May 11, 1988; Chairman, Senator John Melcher

My name is Dr. George Glenner and I am a Research Professor of Pathology at the University of California, San Diego, School of Medicine and Chairman of the California State Task Force on Alzheimer's Disease.

The number of people with Alzheimer's disease is expected to triple within the next 15 years. The cost to families and taxpayers to care for the 2-3 million victims of this disease is presently estimated at 48 billion dollars. This is more than the total cost for care of heart disease, cancer and stroke combined- the three leading causes of death in the United States. If we do not find the cause and cure of Alzheimer's disease, the fourth most common cause of death, the cost for caring for its victims by the year 2,000 will be over $144 billion. If it were possible to ignore the emotional and physical toll on the victims and their families, which we cannot, the impersonal economic facts are that Alzheimer's disease alone could grease this country's slide into bankruptcy. If nothing else, these facts alone should set the biomedical research funding priorities for our Federal government.

Isolation of the Silk Fiber Protein of Alzhiemer's Disease

Since Alzheimer's disease is not caused by aging, yet, much like diabetes and many other disease processes, increases in incidence with advancing age, we describe it as age-related. However, it has been proven to affect individuals as young as 38, and occurrence in the 40s and 50s is not uncommon. Our specific study of Alzheimer's disease began in my laboratory in 1979 at the National Institutes of Health (NIH). Although the lesions of "senile" plaques and neurofibrillary tangles were related as hallmarks to the disease in 1907 by Alois Alzheimer, we were able to show that another lesion involving the blood vessels in the brain was an almost invariable concomitant of this disease. This involvement of the blood vessels was caused by the deposition of silk-like fibers called amyloid. These accumulations of fibers weaken the involved blood vessels causing plasma to leak into the brain and in about 20% of cases cause cerebral hemorrhage from rupture of the weakened vessel. The "senile" plaques and the

neurofibrillary tangles also are now known to be composed of these amyloid silk fibers. In 1970 our laboratory at the NIH was the first to describe the chemical composition of such fibers in a lethal disease process called "systemic amyloidosis" and with this knowledge we were able to determine the chemical nature of this disease.

When our laboratory moved to the University of California, San Diego in 1980, we determined that the next step was to isolate the silk fibers of the brain's blood vessels in Alzheimer's disease in order to analyze them chemically and, thus, possibly to determine their origin and cause. In 1984 our laboratory isolated the silk fiber (amyloid) protein of these blood vessels in Alzheimer's disease and obtained the sequence of the amino acids composing it, i.e. its chemical signature. A computer search revealed this to be a new, previously undescribed and novel protein and it was designated "beta protein". This protein was also found to compose the amyloid fibers of the "senile" plaque. Since plaques and tangles and, as we later found, deposits of amyloid in cerebral vessels occur also in all cases of individuals over 40 years of age having Down's syndrome (the most common cause of mental deficiency in children), and thought to be the result of an extra copy of chromosome 21, we decided to isolate the silk fibers in the blood vessels in autopsy cases of adult Down's syndrome. The protein of the silk fibers from the blood vessels of adult Down's syndrome was essentially identical to the β protein of Alzheimer's disease. This finding irrevocably linked Alzheimer's disease to Down's syndrome and this protein to the abnormal Down's triple chromosome 21. We, therefore, predicted that the gene coding for this protein would reside on chromosome 21. Down's syndrome would then be the first predictable model for Alzheimer's disease.

Indeed within 4 years three groups independently identified the amyloid β protein gene to be on chromosome 21. This gene codes for a larger (precursor) protein of which β protein is a small segment. This parent protein appears to function as a part of cell membranes and, when digested by enzymes, a segment is converted into a regulator or hormonal protein. When improperly digested, i.e. by an abnormal enzyme, the β protein portion of the parent molecule forms amyloid silk fibers in the substance, vessels and nerve cells of the brain.

These latter studies, which were supported by a research grant from the National Institute on Aging, NIH, strongly suggest that there exists an abnormal gene coding for an enzyme which is defective and causes improper cleavage of the ß protein precursor leading to the silk fibers in the plaques and in the brain's blood vessels - thus culminating in Alzheimer's disease. Independent studies indicate a genetic marker for familial (inherited) Alzheimer's disease also to be present on chromosome 21. It is this genetic marker site that may contain the gene for the presumptive abnormal enzyme implicated by us in Alzheimer's disease. If such a theory is proven correct by the finding of a defect in an enzyme digesting the amyloid ß protein precursor, then therapeutic approaches to Alzheimer's disease should readily follow as should definitive diagnostic tests (which presently do not exist) for this disease. The most obvious treatment would be to inhibit the action of the abnormal enzyme and prevent it from forming amyloid fibers from the ß protein precursor. A diagnostic test for Alzheimer's disease would, according to this scenario, result by the specific identification of the abnormal enzyme in blood or tissues of suspected Alzheimer's disease victims.

We are very optimistic, if research funding increases, that within the foreseeable future both a diagnostic test and a treatment for Alzheimer's disease will be found.

Care Research: Model Programs

If indeed Alzheimer's disease were cured today, it would be 20 years or more before the last traces of its devastation and the need for care would have disappeared. Though the results of research have been said to be in the future, and that future is now, we must still provide care for the living, the victims of irreversible brain damage, the dehumanized specters of our mothers and fathers, aunts and uncles and, but for the grace of God, ourselves.

To care for the living victims of Alzheimer's disease and to give respite to their exhausted families an Alzheimer's Family (Day Care) Center was established in San Diego in October 1982. It is affiliated with the UCSD School of Medicine and supported by patient's fees, corporate donations, individual contributions and a California State grant. It is a medical/social model for adult

day care. Neither Medicaid, Medicare nor private insurance covers its costs which are to provide professional care, restore self-respect and dignity to the Alzheimer's victim and mental, physical and financial relief to the caregiver. The Alzheimer's Family Center has cared for over 600 demented victims during its 6 years of operation. It is estimated that this program saves the family about $26,000 per year as compared to nursing home placement - one of the most cost effective community services available.

Cost-Effectiveness

Hypothetical Case: based on 2 days participation at Center for a year

2 days at $30 per day:	$ 60.00
4.4 weeks per month:	$ 264.00
12 mos. participation:	$3,168.00

San Diego average cost of Skilled Nursing Facility, 1 year:	$30,000
Minus Day Care cost per 1 year:	-3,168
Savings:	$26,832

This program has expanded to two additional Centers in the North and East of San Diego County. It is considered a prototype and model for respite day care for Alzheimer's disease patients and has been featured in NEWSWEEK, LIFE, and WOMAN'S DAY magazines and the Congressional Office of Technology Assessment's comprehensive report entitled "Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease".

Programs for adult day care, such as the Alzheimer's Family Center, should be federally funded as research and demonstration projects to confirm their cost effectiveness and should be initiated throughout the United States, and their eligibility for Medicare/Medicaid reimbursement established. We can no longer permit our basic science research nor our community health care systems for Alzheimer's disease to limp along outside of the mainstream of federal funding for health and human services.

If our mission is to raise the standard of living of our ever increasing population of elderly citizens and provide them with respect and dignity, then a necessary corollary is that we also embrace those of our elderly who are stricken in their twilight hours by a dehumanizing disease, and also give them the same share of care and dignity. This is how our society should be measured.

The CHAIRMAN. Thank you Dr. Glenner. Do I understand that you head the California Task Force?

Dr. GLENNER. Yes, that's correct. I'm serving on the California Task Force on Alzheimer's disease.

The CHAIRMAN. That means it involves a large group. You're at the University of California at San Diego, but what does that mean to be Chairman of the Task Force?

Dr. GLENNER. It means that I am 1 of 12 people who are involved in making decisions as to what will be in the report that covers the entire realm of Alzheimer's disease, from its financial deprivations to its research thrust, to the care problems, the legal problems that are involved in Alzheimer's disease, and then to the attempts to educate and train individuals in the care of Alzheimer's patients.

The CHAIRMAN. You are also the founder of what is known as the Alzheimer's Family Day Care Center, which I believe is located in San Diego. Is that correct?

Dr. GLENNER. That's correct.

The CHAIRMAN. We're very much interested in that and in your success in San Diego in the Day Care Center for Alzheimer's because we feel, on this committee, we can best emphasize value of dollars invested in care of the elderly in many instances with day care centers.

Could you just briefly outline what it means to a family with someone afflicted with Alzheimer's. No. 1, what is the satisfaction, for the patient and for the family? And, what is the cost factor? I assume there are significant savings.

Dr. GLENNER. The significance in terms of the family and the patient are two-fold. The family obtains respite, which means they are able to get away for the first time from what amounts to the description of a 36-hour day. They are able to visit friends, go back to a job again, to make doctor's appointments for themselves, or go shopping. So, for 8 hours they are free from having to take care of a patient who may be at home, violent. We are able to reduce the jailed-jailor syndrome in which the caregiver has to lock the doors to keep the patient in.

Interestingly enough, we find that almost invariably the patient objectively gets better after they have come to the day care center. Frequently, they begin to communicate again. Actually some of them start playing the piano again if they had that capability before. We find the reason for this—obviously we are not doing anything to the plaques and tangles—is that we are doing a lot for their depression, which all patients come into the center with—a depression that is induced by the disease.

Once we can strip that depression off by a lot of attention and activities that keep the patient constantly involved, not to the extent that they're overstimulated because that's counterproductive, but they are stimulated to the extent that they perform at an optimum level. We can do that with a lot of tender loving care and the patients do get overtly and objectively better. They are improved. And they go back home improved, which makes the family feel so much better because something obviously has been done for them.

We teach the family how to take care of the patient when they're home. We do intervene to try to, successfully much of the

time, prevent incontinence by having a schedule for the patient. We teach that to the family. We have a teaching program now for both nonprofessionals and general health professionals on how to deal with Alzheimer's patients. We have a video-tape we'd be very happy to give you on that particular program.

We have three day care centers in San Diego County. They are located in major areas where there are many dementia patients.

The CHAIRMAN. Are those three just for Alzheimer's?

Dr. GLENNER. We call them the Alzheimer's family centers, but they are not just for Alzheimer's Multi-infarct dementia individuals are there. We have Parkinson's patients. We have had an occasional psychiatric patient.

The CHAIRMAN. The alternative to what you describe, and I picture a very accurate description of the 36-hour day for the caretakers of Alzheimer victims, would be the nursing home.

Dr. GLENNER. That's right. It is very expensive. We have the figures in our written testimony.

The CHAIRMAN. Yes, I think they're in the testimony. Roughly $25,000–$30,000 a year for nursing home care.

Dr. GLENNER. The average cost of a skilled nursing home per year in the county of San Diego is $30,000. If we subtract the cost of going to the day care center for 2 days a week at $30 per day, the total savings for the year would be $26,832 for that patient, for that family.

The CHAIRMAN. That's fantastic.

Dr. GLENNER. It's staggering.

The CHAIRMAN. When you identified the amyloid—as I understand this correctly, but I'm not sure I do and I want to ask you to enlighten me—you say it's a means of diagnosis. How do you do it exactly? Do you remove some tissue from the brain of a patient? How do you identify if somebody has the amyloid present in the walls of the arteries or blood vessels? I guess they're arteries, are they not?

Dr. GLENNER. All vessels, capillaries, veins and arteries.

The Chairman. It could be any vessel then?

Dr. GLENNER. Right.

The CHAIRMAN. How do you do that?

Dr. GLENNER. It could be done by brain biopsy. Brain biopsy is not normally done in a condition where there is irreversible dementia, because it is not usually a question of can you treat it. So if you can't treat something, the diagnostic part of it does not seem to spur people to do brain biopsies. There have been arguments however, that it should be done in all cases of dementia. In practice, the definitive diagnosis is only at autopsy.

The CHAIRMAN. It's only done at autopsy. Then it's not done on a living person?

Dr. GLENNER. No.

The CHAIRMAN. It contributes to the research of it, but so far the diagnosis of Alzheimer's is by symptoms.

Dr. GLENNER. Eventually, I feel that the research studies I described will lead to a diagnostic test during life.

The CHAIRMAN. Oh, you feel it will lead to it.

Dr. GLENNER. It will lead to a diagnostic test when we find what we believe to be the abnormal protein or enzyme, that makes the

silk fibers. Basically, we are looking at a diagnostic test for an abnormal protein or enzyme. If it exists, we should be able to find it in the serum and possibly in peripheral tissue.

The CHAIRMAN. Are we going to go to the biochemist and the molecular scientist?

Dr. GLENNER. That's right.

The CHAIRMAN. Thank you. Dr. Kritchevsky, I don't know whether other witnesses touch on nutrition or not, but the preventive aspects of good nutrition I find to be very encouraging.

What do you mean when you say nutritional assessment?

Mr. KRITCHEVSKY. It's finding if there are deficient in any specific trace minerals or vitamins, which is what we have done at all age groups up to about 50 or 60. If you look at recommended allowances, they have them for infants, for children, for teenagers, and for adults. Then at about 50 or 60, they just say 50 plus.

I think what we have to do is start making these kinds of assessments, and they are being made, for people in their 60's, 70's, and 80's. They may all be individuals, but then you can tailor it. With the difficulty or reduced capacity for absorption, and based on differences in diet, they may just be absorbing less iron than they need let's say, or less calcium, or some other trace mineral.

The CHAIRMAN. Are you recommending for a first step then to find out what is happening in older people? Is that it?

Mr. KRITCHEVSKY. I would say describe "normal."

The CHAIRMAN. Describe "normal." At what age, though?

Mr. KRITCHEVSKY. Well, I think you're going to have to do it for several ages, possibly 60, 70 and 80.

The CHAIRMAN. And that's not done yet?

Mr. KRITCHEVSKY. It's being done. It's being vigorously worked on, but there just aren't yet enough data. The U.S. Department of Agriculture's Aging Institute at Tufts University is doing a lot of work on this; I'm sure that it will emerge pretty soon.

But our aging population is so diverse. You have people of such different backgrounds and in so many different areas, that we possibly are going to have to start from scratch, you know, because it is a function of what people eat. Some people, because of ethnicity or religion may not eat the kind of foods that everybody else eats. Eventually, I think we will emerge with a picture of what the average levels of these substances in the blood are and what we have to supplement them with. I am very hopeful that this will occur in a very short time because there is a lot of effort going into it.

The CHAIRMAN. When you say a lot of effort, let's translate it into dollars.

Mr. KRITCHEVSKY. I'm afraid I can't do that. Whenever you talk to researchers, whenever you mention dollars, that strikes a responsive chord that is nowadays a minor chord. There is a lot of work in this particular area sponsored by the USDA, and there are lot of people trying—for instance, the NHANES, which is the National Health and Nutrition Experimental Survey, is getting a lot of information from interviews with people all over the United States.

They are taking a diet recall and assessing this through computerized data as to what they eat. For instance, they suggest that men over 65 should get something like 2,050 calories a day and

women about 1,500. In reality, the NHANES show that men get about 1,800 calories and women about 1,300. This may be somewhat on the low side because one of the problems is that when you get fewer calories even if you are eating a well rounded diet, you may have fewer of the nutrients that come with specific foods.

The CHAIRMAN. I think you are all aware that each of us on this committee serves on other committees. Earlier, Senator Domenici referred to what was being done in the Department of Energy concerning mapping the genome. I serve on that committee, as does Senator Domenici.

I also serve on the Agriculture Committee. I'm well aware of the limitations on the Department of Agriculture and the amount of research dollars they have. When it comes to nutrition, the Agriculture Department frequently takes the lead because of their responsibility for the school lunch program, senior citizen nutritional programs, and food stamps. There is a broad variety of responsibility that Agriculture has, so I am not surprised when you mention that they are taking the lead in nutritional research. I am also aware that those dollars are pretty limited.

You said a low chord, so naturally you would recommend more. But how much more can we do wisely?

Mr. KRITCHEVSKY. I think that, for instance, most of the research funding in this country comes from the National Institutes of Health. It is generous in several senses, one of which is that the funding is given for ideas, and not really directed because the general feeling is that the investigators know what to do.

One of the problems with applying for research funds in nutrition is that they all, go to the same body, like the study section. For instance, the area of nutrition and heart disease is far ahead in knowledge of the area of nutrition and cancer which, in turn, is somewhat ahead of the area of nutrition and aging.

So, by the very essence of the way these grants are written, the grant applications in these areas other than heart, sound like high school projects compared to the very sophisticated work that is going on in nutrition and heart disease. My own feeling is that there should be some way of judging the grants based on what they represent to the particular field, rather than judging them against each other.

The CHAIRMAN. I am delighted that you are on this witness list because with this type of thing, when you don't have the basics done, it isn't that costly to get them done. I guess that's what you're advocating. Discover what would be the normal for age 60 to 65, 65 to 70, and so on. Is that correct?

Mr. KRITCHEVSKY. Yes. I also would like to say that one of the other problems is that in animal research, if you're talking about aging research, it is very long-term research which sometimes goes beyond the limits of ordinary funding. Usually it's 3 to 5 years. If you have these animals that last 5 or 6 years, you don't have enough data to write a report when the next application is due.

The CHAIRMAN. What do you want us to do then?

Mr. KRITCHEVSKY. I think, in general, as I said, it should be——

The CHAIRMAN. Should it be multi-year funding?

Mr. KRITCHEVSKY. Well, depending on the type of work. Some things can be done relatively quickly, but if you're going to study

aging in a species that takes a number of years, you have to be prepared to wait that long for some kind of result.

The CHAIRMAN. Simply put, that does mean multi-year funding then, does it not? Multi-year commitment?

Mr. KRITCHEVSKY. Yes. More years. Generally now the grants are three to five years. For most research projects, they are adequate. As an example, we do work on the effective caloric restriction on experimental tumors in rats. We find that if we reduce calories, we get few tumors, regardless of what we feed them. One question that has to be answered—and the way these experiments are done, let me interject, is you terminate the experiment at a specific point in time because that's the way it is always done. The question that is not answered is, supposing we let all of these rats live to their projected lifespan. Will the ones who are calorically restricted catch up, or would this diminution in tumors hold during their entire life span?

The CHAIRMAN. I understand your point. Thank you both very much.

Mr. KRITCHEVSKY. Thank you.

Dr. GLENNER. Thank you.

The CHAIRMAN. Our third and last panel today deals with immune modifiers. Dr. Takashi Makinodan, Director of Geriatric Research, Education and Clinical Center, Veterans' Administration, Wadsworth Medical Center, Los Angeles, CA; Dr. Gino Doria, Euratom Biological Division, Laboratory of Radiobiology from Rome; and Dr. William Ershler, Director of Gerontology from the University of Wisconsin Medical Sciences Center in Madison.

Please be seated, doctors. I believe you are first, Dr. Makinodan.

STATEMENT OF TAKASHI MAKINODAN, PH.D., DIRECTOR, GERIATRIC RESEARCH, EDUCATION AND CLINICAL CENTER, WEST LOS ANGELES VA MEDICAL CENTER AND DEPARTMENT OF MEDICINE, UCLA, LOS ANGELES, CA

Mr. MAKINODAN. My name is Takashi Makinodan. I am the Director of the Geriatric Research, Education and Clinical Center of the West Los Angeles VA Medical Center and a Professor of Medicine in Residence at UCLA. I am also an immunologist and I have been involved in research in immunity and aging for over 20 years.

This morning, I wish to comment on the loss of immunologic vigor with age; i.e., as individuals age, they lose their ability to resist certain infections and destroy certain cancer cells. The clinical consequences of loss of immunologic vigor is a greater vulnerability to diseases which begins in humans after age 60, and increases exponentially thereafter.

In order to develop strategies to restore immune functions of the elderly, we first focused our effort by identifying the specific immune cells which are vulnerable to aging. These cells indicated that aging affected the T cells, the same cells that are destroyed by the AIDS virus. Furthermore, by peering into these T cells, we found that the molecular machineries are altered.

Since the task of repairing molecular damages is quite formidable, we decided to learn more about the thymus, the generator of T cells. These studies emphasized the need to learn how to "turn on"

the aging thymus to function normally. If successful, we will be able to replace at will the senescent T cells of the elderly with new T cells. No doubt, the resolution of this task will require much effort and time.

In the meantime, we and others have learned that immune cells are most accessible for intervention to reduce or reverse the deleterious effects of aging.

Thus, for example, my colleagues and I have succeeded in rejuvenating the immune response of old mice by implanting into them marrow and thymic cells from young animals. We have also been successful by giving them immunopotentiating agents. Others have been successful by dietary manipulation, or by giving them the hormones of the immune system. Such findings are most encouraging, for they suggest that acute and chronic catastrophic illnesses facing the elderly could be reduced significantly, if effective methods can be developed to restore the immune functions of, for example, 75-year-old individuals to the level of 30-year-old individuals.

At least two options are now available in restoring the immune functions of the elderly: One option is to cryogenically preserve one's own marrow and T cells while in good health in the event that transplantation therapy will be shown to be effective in humans; another option is to artificially replace the thymus with the hormones that promote growth of T cells.

I believe we are now near the brink of major breakthroughs in restoring the waning immune functions of the elderly. This means that, so far as the immune system is concerned, we are close to fulfilling a response to a plea that you, Mr. Chairman, and your colleague, Senator John Heinz, made in 1986, and I quote:

> The greying of America presents us with significant challenges and opportunities. Providing for the health, income, and housing needs of this ever-growing older population are only a few of the challenges. We must also seek better ways to enable older Americans to remain productive and independent. The greatest challenge then, is to expand opportunities to put to use the full talents of this vast resource so that the promise of long life is worth living.—John Melcher, Chairman; John Heinz, Ranking Member.

I wish to emphasize that my work on the immune system of the elderly is but one example of how basic research can eventually improve the medical care of the elderly. Therefore, as a member of the research committee, I strongly recommend the need for a substantial increase in the research budget for aging, especially since the cost of translating basic research findings into cost-effective geriatric health care delivery practice is very high.

Thank you for permitting me to present my views.

I appreciate this opportunity to testify.

[The prepared statement of Mr. Makinodan follows:]

ORAL TESTIMONY BEFORE THE U.S. SENATE SPECIAL COMMITTEE ON AGING

TAKASHI MAKINODAN, Ph.D.

VA Medical Center West Los Angeles and Department of Medicine, UCLA

Los Angeles, CA

May 11, 1988

Mr. Chairman and Members of the Special Committee on Aging:

It is a privilege to be given the opportunity to discuss our research on aging.

I wish to begin this testimony by introducing myself. I am an immunologist by training and have been involved in research in immunity and aging for over 20 years. Twelve years ago, I joined the Veterans Administration as the Director of the Geriatric Research, Education and Clinical Center (GRECC) of the West Los Angeles VA Medical Center and joined UCLA as Professor of Medicine in Residence. One of the attractive features of GRECC is the opportunity to integrate basic research activities on aging with those on geriatric health care delivery. This provides a mechanism by which basic scientists can present their findings to geriatricians for their clinical consideration. In turn, geriatricians can present their pressing clinical problems to basic scientists to stimulate collaborative research. Thus, in the GRECC environment, discussions between the scientists and the health care professionals occur frequently on an informal, day-to-day basis in a setting where the urgency of the problems of aging is appreciated.

Within the time allotted to me, I wish to comment on our recent findings on the cellular basis for loss of immunologic vigor with age, i.e., as individuals age, they lose their ability to resist certain infections and destroy certain cancer cells. Such information is valuable for the development of ways to either retard or restore immune functions in the elderly.

Aging in humans and animals is associated with a progressive loss of immunologic vigor. The clinical consequence of this process is a greater vulnerability to diseases which begins in humans after age 60 and increases exponentially thereafter. Fortunately, the immune cells are most accessible for intervention to reduce or reverse the deleterious effects of aging. Thus, for example, my colleagues and I have succeeded in rejuvenating the immune response of old mice by implanting into them marrow and thymic cells from young mice. Because genetically inbred strains of mice were used, there was no rejection problem. We have also been successful by giving them immunopotentiating agents. Others have also been successful by giving lymphokines, the hormones of the immune system. Such findings are most encouraging, for they suggest that acute and chronic catastrophic illnesses facing the elderly

could be reduced significantly if effective methods can be developed to restore the immune functions of, for example, 75 year old individuals to the level of 30 year old individuals.

In order to develop better strategies to restore immune functions of the elderly, we began by focusing our effort at the cellular level by identifying the specific immune cells which are vulnerable to aging. These studies indicated that aging affected the T cells, the same cells that are destroyed by the AIDS virus. Thus, changes could be seen in the T cells which are specialized to kill tumor cells and virally-infected cells and also in T cells which are specialized to regulate various immune functions. Furthermore, by peering into these T cells, we found that their molecular machineries are altered.

Since the task of repairing molecular damages is quite formidable, we decided to learn more about the thymus -- the generator of T cells. Specifically, we began by searching for a functional marker associated with the aging thymus. We found that the decline in the ability of the thymus to produce T cells with age was linked to the production of an inhibitor of thymic T cell growth. These findings emphasize the need to learn how to "turn on" the aging thymus to function normally. If successful, we will be able to replace at will the damaged T cells of the elderly with new T cells. No doubt, the resolution of this task will require much effort and time. In the meantime, two options are now available in restoring the immune functions of the elderly. One option is to cryogenically preserve one's own marrow and T cells while in good health, in the event that a transplantation therapy will be shown to be effective in humans. Another option is to artificially replace the thymus with lymphokines that promote the growth of T cells. In this regard, it is most gratifying that my colleagues, Drs. William Ershler of the University of Wisconsin and Allan Goldstein of George Washington University, have been engaged in a monumental task of potentiating the immune functions of the elderly with use of certain thymic hormones, the thymosins.

In summary, I believe that we are now near the brink of major breakthroughs in restoring the waning immune functions of the elderly. This means that so far as the immune system is concerned, we are close to fulfilling a response to a plea that you and your colleague, Senator John Heinz, made in 1986 (S. Doc. 100-8, Developments in Aging: 1986, vol. 1):

> The greying of America presents us with significant challenges and opportunities. Providing for the health, income, and housing needs of this ever-growing older population are only a few of the challenges. We must also seek better ways to enable older Americans to remain productive and independent. Our greatest

challenge then is to expand opportunities, to put to use the full talents of this vast resource so that the promise of long life is worth living.

John Melcher,
Chairman.
John Heinz,
Ranking Member.

I wish to emphasize that my work on the immune system of the elderly is but one example of how basic research can eventually improve the medical care of the elderly. Therefore, as a member of the research community, I strongly recommend the need for a substantial increase in the research budget for aging, especially since the cost of translating basic research findings into cost-effective geriatric health care delivery practice is very high.

Thank you for your courtesy in permitting me to present my views, and I would be pleased to answer any questions you may have.

The CHAIRMAN. Thank you, Doctor.
Dr. Doria.

STATEMENT OF GINO DORIA, M.D., LABORATORY OF PATHOLOGY, C.R.E. ENEA, CASACCIA, ROME, ITALY

Dr. DORIA. Mr. Chairman, my name is Gino Doria. I am a Professor of Immunology and the Head of the Immunology Group at the Energy Research Center of ENEA at Casaccia, near Rome, Italy. It is for me a privilege to testify before this committee on advances in aging research.

For the sake of brevity, I will abstract my full written testimony.

My area of expertise is experimental immunology and I have been engaged for many years in studies of immunoregulation of the antibody response in aging.

During senescence, the immune system undergoes profound alterations associated with a progressive decline of immune responsiveness to pathogens and increasing incidence of autoimmune phenomena. Most of the major diseases observed in senescence have an immunological pathogenesis associated with these alternations. Immunodeficiency and autoimmunity are preceded by involution of the thymus gland and arise from changes in thymus-dependent T lymphocyte populations that regulate the immune response.

The first strategy of intervention we adopted was the administration of synthetic thymic hormones to counteract the effects of thymic involution and to correct age-related alterations of immunoregulation.

We found that the injection of these molecules in old individuals restores T cell functions up to the levels observed in adulthood. In our subsequent studies, similar results were also observed after the injection of interleukin 2 or gamma interferon.

The results from our studies are still preliminary, but indicate that administration of synthetic thymic hormones, interleukin 2, or gamma interferon can restore to normality important immunological functions impaired by aging. The use of these molecules, collectively denominated "biological response modifiers," is promising, but requires very accurate protocols to reach two antithetic objectives, such as an increased immune responsiveness against pathogens and the prevention or mitigation of autoimmune reactions.

It is likely that these powerful new medicines may prevent or correct alterations of the normal balance of immune functions which might be instrumental to prolong the duration and improve the biological quality of life.

Long-term studies in our laboratory, in cooperation with the Fondation Curie in Paris, have already shown that the same set of genes that determines high immune responsiveness in mice also increases longevity and decreases tumor incidence.

Another long-term research now in progress with the cooperation of the Department of Biochemistry at the George Washington University, aims at demonstrating the possibility to prolong life span and to reduce tumor incidence in mice by thymic hormone treatment applied before the appearance of the age-related decline of immune functions.

It is certainly desirable, and perhaps necessary to foster cooperative ventures to tackle research problems which single laboratories, and in some cases single countries, are unable to solve satisfactorily, owing to the uneven distribution of imagination, talent, funds, and efficient administration. "The Last Emperor," a movie by Bernardo Bertolucci, may be taken as a recent example of great achievement by multinational cooperation in a different area of human creativity.

It is my hope that following the examples of ongoing fruitful cooperation in aging research, specific biomedical programs be carried out by several countries in a world-wide common effort.

WHO may establish a coordinating structure to facilitate international cooperation among research groups and reference laboratories. This cooperation should focus on cross-sectional and longitudinal studies to develop standardized methodology and research protocols to assess the change in immune functions in aging without associated diseases.

Essential prerequisites for many of these studies are the conservation and distribution of biological materials, as well as the maintenance of common inbred animals in a few international locations to enable investigators of different laboratories to use aging animals of the same genetic background and raised under the same environmental conditions.

Reference values of immune functions in aging, as obtained from studies of populations under different socioeconomic and nutritional conditions, together with comparative life span and morbidity data collected from an international study population, serve a twofold purpose: They help to disentangle genetic from environmental effects; they assist in designing intervention strategies to endeavor successful applications of biological response modifiers for prevention or therapy of immune dysfunction in aging and, perhaps, of aging itself.

This concludes my testimony. I would be happy to answer questions.

[The prepared statement of Dr. Doria follows:]

MR. CHAIRMAN AND DISTINGUISHED MEMBERS OF THE U.S. SENATE SPECIAL COMMITTEE ON AGING.

My name is Gino Doria. I am a Professor of Immunology and the Head of the Immunology Group of the Pathology Laboratory at the Energy Research Center of ENEA at Casaccia (Rome), Italy. My research is supported jointly by ENEA and by the Commission of the European Community of which I have been an employee since 1962. It is for me a privilege to testify before this Committee on advances in aging research.

My area of expertise is experimental immunology and I have been engaged for many years in studies of immunoregulation of the antibody response. During the last two decades these studies expanded to a considerable extent in the United States as well as in Europe and provided rapidly growing information for a better understanding of immunity at the cellular and molecular level. Thus, it has become very clear that the expression of the immune functions against exogenous antigens, as in immunity to pathogens, and against self antigens, as in autoimmunity, is regulated by a complex network of cellular and molecular interactions. The main cell types involved in this regulation are the T lymphocytes that exert either helper or suppressor activity on the immune response. T lymphocytes are so denominated after their origin from the thymus gland in which , under the influence of thymic hormones, they acquire functional maturity. After migration from the thymus to the peripheral lymphoid tissues mature T cells exert regulatory functions on other cells of the immune system by cell to cell interactions and by secreting and responding to powerful immunoregulatory molecules such as interleukins and interferons.

During senescence the immune system undergoes profound alterations associated with a progressive decline of immune responsiveness to exogenous antigens and increasing incidence of autoimmune phenomena. These alterations are preceded by involution of the thymus gland and arise from changes in regulatory T cell populations.

Immunologic alterations seem to play a major role in the biological processes of aging. The maximum life span has, indeed, been shown to be significantly influenced by genes of the major histocompatibility complex which controls immunoregulatory cell functions. Furthermore, most of the major diseases observed in senescence have an immunological pathogenesis associated with a decline of immune responsiveness and increased propensity to autoimmune reactivity. A link between immunodeficiency and the increase of tumor incidence with advancing age has also been proposed.

The first strategy of intervention we adopted was the administration of thymic hormones to counteract the effects of thymic involution and to correct age-related alterations of immunoregulation. After a few initial trials with extracts from the calf thymus we proceeded to use synthetic thymic hormones, such as thymosin α_1 and thymopentin, in mice and humans. We found that injection of these molecules in old individuals restores T cell functions up to the levels observed in adulthood. Most of our studies were carried out in old mice and demonstrated that injection of thymosin α_1, a synthetic 28 aminoacids peptide, increases the frequency of T cell precursors, helper T cell activity, interleukin 2 production and expression of cell receptors for this lymphokine. In our subsequent studies some of these effects were also observed in mice injected with interleukin 2 or gamma interferon.

The results from our experimental and clinical studies are still preliminary but indicate that injection of synthetic thymic hormones, interleukin 2, or gamma interferon can restore to normality important immunological functions impaired by aging. The use of these molecules, collectively denominated "Biological Response Modifiers", is promising but requires very accurate protocols to reach two antithetic objectives, such as an increased immune responsiveness against exogenous antigens and the prevention or mitigation of autoimmune

reactions. It is likely that these powerful new medicines may prevent or correct alterations of the normal balance of immune functions which might be instrumental to prolong the duration and improve the biological quality of life.

Long term studies in our laboratory, in cooperation with the Fondation Curie in Paris, have already shown that the same set of genes that determines high immune responsiveness in mice also increases longevity and decreases tumor incidence. Another long term research, now in progress with the cooperation of the Department of Biochemistry at the George Washington University, aims at demonstrating the possibility to prolong life span and to reduce tumor incidence in mice by thymosin α_1 treatment applied before the appearance of the age-related decline of immune functions.

It is certainly desirable and perhaps necessary to foster cooperative ventures to tackle research problems which single laboratories and, in some cases, single countries are unable to solve satisfactorily, owing to the uneven distribution of imagination, talent, funds, and efficient administration. "The Last Emperor", a movie by Bernardo Bertolucci, may be taken as a recent example of great achievement by multinational cooperation in a different area of human creativity.

Scientific cooperation exists at the European Community level and is stirred by the concerted action of the 12 Member States in which the appointed authorities, for Italy the Consiglio Nazionale delle Ricerche and the Istituto Superiore di Sanita', insure the implementation and coordination of the national contributions to concerted biomedical programs. The co-ordinated program dealing with age-related health problems (EURAGE) for 1987-89 includes: 1) Aging of crystalline lens. 2) Changes in immune response. 3) Drug metabolism in elderlies. 4) Brain aging and senile dementia. 5) Animal facilities.

It is my hope, however, that following the examples of ongoing fruitful cooperation in aging research, specific biomedical programs be formally extended well beyond the EURAGE boundary to bridge other countries in a world-wide common effort. Switzerland, Sweden, Austria,

Israel and the United States have already expressed their willingness to participate. WHO may establish a coordinating structure to facilitate international cooperation among research groups and reference laboratories. This cooperation should focus on cross-sectional and longitudinal studies to develop standardized methodology and research protocols to assess the change in immune functions in aging without associated diseases. Essential prerequisites for many of these studies are the conservation and distribution of biological materials as well as the maintenance of common inbred animals in a few international locations to enable investigators of different laboratories to use aging animals of the same genetic background and raised under the same environmental conditions. Reference values of immune functions in aging as obtained from studies of populations under different socioeconomic and nutritional conditions together with comparative life span and morbidity data collected from an international study population serve a twofold purpose. They help to disentangle genetic from environmental effects and they assist in designing intervention strategies to endeavor successful applications of biological response modifiers for prevention or therapy of immune dysfunction in aging and, perhaps, of aging itself.

The CHAIRMAN. Thank you Doctor.
Dr. Ershler.

STATEMENT OF WILLIAM B. ERSHLER, M.D., DIRECTOR OF GERONTOLOGY, ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF WISCONSIN MEDICAL SCIENCES CENTER, MADISON, WI

Dr. ERSHLER. Senator Melcher, Senator Pressler, thank you for the opportunity to speak at this important committee here.

My name is William Ershler. I am an Associate Professor of Medicine at the University of Wisconsin in Madison. Please consider my comments as those of an individual who is actively involved in both biological research in aging, and in clinical medicine.

Despite the clinical advances of the past century, infections remain a major cause of illness in elderly people. For example, influenza occurs more frequently in the elderly, is more severe, and is often an antecedent of bacterial pneumonia and death. It is reasonable to assert that age-related immune deficiency, or immune senescence, contributes to the predisposition to infection.

Immune senescence occurs in all mammalian species and in humans the decline is most notable in the thymus dependent, or T cell component of the immune response. T cells are those white blood cells that are important in our defense against most viruses and tumors and a T cell deficiency certainly may be causally related to an increased incidence of viral infection and cancer, both of which we observe in aging.

As mentioned, a very common infection is influenza which remains a major cause of morbidity and mortality in elderly populations. Like several other viral infections, it is likely that age-related immune deficiency contributes to the predisposition to influenza. Despite the fact that influenza vaccines are commercially available, their utility has been hampered by the relatively weak ability to stimulate antibody. This may occur even with young, immune, competent recipients.

Another factor that may account for the lack of effectiveness of the vaccine is the inability of many, if not most, old people to mount a sufficient antibody response to the vaccine to protect them from the infection. Failure to produce antibody could well explain the clinical observation of influenza infection in individuals who have been vaccinated. It is estimated that from 25 to 50 percent of elderly people who do not achieve the four-fold increase in the antibody level that, by convention, is considered the definition of a vaccine response, and presumably protection.

To date, there has been no proven method of increasing vaccine efficacy, although there are certain leads that sound promising. We are pursuing a line of research at the University of Wisconsin that we expect will ultimately result in enhanced capabilities of preventing influenza, and perhaps other infections in elderly people.

We had previously shown that antibody production to the influenza vaccine could be enhanced in the test tube by the addition of thymic hormone to the cultured cells. We had also previously demonstrated this to be true to tetanus toxoid antibody production.

The thymic hormone preparation, Thymosin Alpha One, is a purified protein hormone that Dr. Goldstein had discussed. It is a hor-

mone produced by the thymus gland. Its level, like the thymus gland function in general, declines with advancing age. Our observations about enhanced antibody response with thymosin seem logical because of the known requirement of T cell function for antibody production to the flu shot, and the known T cell deficiency associated with the age-related decline of the thymus gland.

We have expanded our early observations to a series of three clinical trials of synthetic Thymosin Alpha One which was kindly provided by Alpha One Biomedicals, Inc., here in Washington, D.C.

The most recently completed trial took place in, and was supported by, the VA Hospitals in the State of Wisconsin. The work was performed in collaboration with my colleagues Dr. Stefan Gravenstein and Ms. Barbara Miller in Madison, and Dr. Edmund Duthie in Milwaukee, Dr. Paul Drinka in King and Dr. Kumara Prathipati in Tomak. Just less than 100 elderly volunteers received either thymosin or placebo in conjunction with the flu vaccine. While less than one-half of those receiving the placebo had a significant rise in antibody level, 70 percent of those that received thymosin did.

We were encouraged by these findings and proceeded to a larger 400-person clinical trial of thymosin the past flu season. This trial was performed in collaboration with Dr. McConnell and Dr. Simon at the George Washington University and my colleagues, Dr. Gravenstein and Ms. Miller at the University of Wisconsin.

The volunteers were all inpatients at the U.S. Soldiers' and Airmen's Home in Washington. Two different doses and schedules of thymosin were compared with placebo in recipients of this year's flu shot.

We haven't completed the analysis—it is going on right now—but if we are able to confirm our previous observations, we will be encouraged that this immunologic reconstitution by thymic hormone, administered in association with the vaccine, may be a research breakthrough that will eventually lead to the reduction of influenza and its associated complications in elderly people.

This type of clinical investigation in geriatric medicine is generally considered lower priority when compared to the more basic and molecular experimentation, and funding has been rate limiting on these type of advances.

I would like to suggest to this committee that the Congress be advised to consider clinical research in aging a high priority.

Thank you. That's the end of my testimony.

The CHAIRMAN. Doctors, I guess it's fair to say you're all immunologists. Is that correct?

Mr. MAKINODAN. Yes.

Dr. DORIA. Yes.

Dr. ERSHLER. Yes.

The CHAIRMAN. Well, I suspect I'm older than any of you. My academic days in Veterinary medicine preceded your academic days. As students, we had to know something about the past of immunology. It always strikes me as sort of a marvelous development of immunology considering that in several centuries, I believe the most advanced immunology was bleeding, was it not? It was causing the patient to hemorrhage, either by cutting into an artery, or some blood vessel, or attaching leaches to the patient in order to

gain the same end. Is that correct? Did you all learn that as I had to learn it?

Mr. MAKINODAN. Before my time. [Laughter.]

The CHAIRMAN. Well, after several centuries of that, now Pasteur seemed to find a way to do something about rabies. Lister, I believe it was, found a way to do something about smallpox. But that must have been about a century ago—a little over a century ago—and it seems to me in the past 50 years, maybe even greater in the past 20 years, immunology has made strides that seem fantastic.

Dr. Doria, you know, we like to say, as you heard earlier in comments made from Senators up here that we are in the forefront in medical research in America. I'm sure we share with medical researchers all over the world, the desire to move mankind forward.

Can you comment to us on how you view the type of research going on in European countries, as compared to the approach to the research here in the United States?

Dr. DORIA. The Member States of the European Community have created a structure, named Eurage, whose task is the implementation and coordination of the national contributions to concerted programs of aging research. The Commission of the European Community provides funds to trigger and make national initiatives more effective in this corrected action. The areas of aging research being covered by Eurage are the immune response, the crystalline lens, the drug metabolism in the elderly, brain aging and senile dementia, and animal facilities.

This last point, for example, as I mentioned in my testimony, is extremely important for experimental immunology. Just to give you an example, the diet restriction in animals, as we have heard previously, seems to be very promising for amelioration of the biological quality of life, and for life span prolongation. But, to raise animals under dietary restriction is quite a task. Therefore, I think that the few existing centers should be potentiated and then become able to distribute these very precious animals to other laboratories which are interested in this kind of research.

I think that the approach that should be adopted is international cooperation, to which each country can contribute by its own expertise, to reach the common goal of preventing or mitigating the pathology of the elderly.

The CHAIRMAN. You mentioned that the European Community pools its resources.

Dr. DORIA. Yes.

The CHAIRMAN. All right. Then, should the World Health Organization be the broad umbrella group, or coordinating group?

Dr. DORIA. Yes, because not only is the European Community involved but also the United States, Austria, Sweden, and Switzerland have already expressed their willingness to participate in the Eurage. So, we would have a broader structure which, in my opinion, could greatly benefit from the intervention of W.H.O. to provide implementation and coordination of national efforts towards common goals which are decided in a concerted action.

The CHAIRMAN. How do we prevent over duplication? By publishing? Can we avoid over duplication of research efforts by publishing articles?

Dr. DORIA. Yes, publishing articles is necessary but not sufficient to prevent useless duplications.

The CHAIRMAN. You would take it one step further and try coordination prior to publication, then?

Dr. DORIA. Correct. Coordination could drive the program to include a larger spectrum of research in each area without too much overlapping.

The CHAIRMAN. I see. In other words, quarantine.

Dr. DORIA. Yes, to some extent.

The CHAIRMAN. And it's possible?

Dr. DORIA. Hopefully, yes. Hopefully.

The CHAIRMAN. I agree with you. Hopefully.

Dr. DORIA. It has been possible in Europe.

The CHAIRMAN. It has been possible in Europe? How many countries are involved in this?

Dr. DORIA. Twelve.

The CHAIRMAN. What do you think of this, Mr. Makinodan? All of you are encouraging more funding, I believe for medical research. Does this idea of coordination through a world health organization make sense to you?

Mr. MAKINODAN. Yes, it does, primarily because research in aging takes so long to complete. Therefore, to maximize the efficiency of research operation, it would be very good if there is a way of sharing information on the progress of investigators. Some of these experiments might take, as Dr. Kritchevsky said, 5 to 6 years to just complete one experiment. Thus, this idea of coordinating on a worldwide basis, would be a very efficient way of implementing research at all levels.

The CHAIRMAN. All three of you are involved in research with thymosin, is that correct? Earlier, we heard from Dr. Goldstein that, in this country at least, a product may be available soon for general use. Is there research going on now connected with the Veterans Administration?

Mr. MAKINODAN. Yes. Dr. Ershler is doing that.

The CHAIRMAN. Doctor, would you agree with Dr. Goldstein that thymosin might be available within 2 years or less? That is, available for therapeutic use in general.

Dr. ERSHLER. Right. I think there are a few obstacles to overcome. We are very encouraged by the studies to date. We have found that in aging as well in the variety of the other immune deficient states for which thymosin has been used, it is to be very safe. We have been very careful to look for signs of toxicity, both immunologic toxicity, if you will, as well as other signs of drug toxicity.

We think that it is effective and we think it could be used soon. There are a few things we are working on now. For example, what's the appropriate dose, and what's the appropriate schedule, and whether or not we need to give it by injection, which is the way the clinical trials have been going to date.

We are currently working in our laboratory on developing an oral formulation because in laboratory animals it turns out that the intact active portion of the molecule makes its way into the bloodstream after an oral dose.

So these are things that need to be worked out, because I don't think older people want to take more shots. If we can get it available in an oral form, that would even make it that much better. I'm not sure exactly how long it takes to get through the process once we have proven it to be effective. That will be an eye opener, I suppose, for me. I think it is almost ready to be presented to the authorities in that light.

The CHAIRMAN. Well, you've proven it to be effective. The tests are to find out whether there are side reactions. Isn't that correct?

Dr. ERSHLER. I think I feel more comfortable that there are no side effects than I do about the efficacy. That's the reason we're doing the large study this current flu season. Although I think that the preliminary data makes us very confident that the larger study will support that. We are quite confident that it's effective.

I think the efficacy is the question now—not the toxicity. It's not just for aging people that it's been tried; many patients have received thymosin before and, in addition patients that had been old have received it. We really have seen no toxicity, so we feel good about that.

That's true also for laboratory animals. We've treated mice in Madison with it, and also monkeys quite extensively. I know that Dr. Doria has had quite a good experience with it in laboratory animals as well. I think it's quite safe.

The CHAIRMAN. Dr. Doria, you also mentioned interleukin 2 or gamma interferon. Neither of those are close to completing the necessary testing for use, are they? Or am I just not informed?

Dr. DORIA. Both interleukin 2 and gamma interferon have been tried in several diseases, especially in the therapy of human cancer. As far as aging is concerned, the experience has been so far with experimental animals. We found that both molecules are very effective when injected into old mice in order to repair the cell functions which have been impaired by aging. I would say that they are extremely effective on a dose basis, so that one can gear very well their effect toward the goal which one is looking for.

The CHAIRMAN. But it is just in the testing state? It has not been applied therapeutically yet in general?

Dr. DORIA. For example, interleukin 2 has been attempted in the therapy of human tumors.

The results are promising, but not completely convincing.

The CHAIRMAN. Is it available commercially?

Dr. DORIA. Yes; it is available for trials. But, I think that it requires many more studies in order to make a safe use of it, because it is rather toxic.

The CHAIRMAN. Has it been approved for therapeutic use by a practitioner?

Dr. DORIA. It is on trial.

Dr. ERSHLER. In the United States, interleukin 2 is being used for cancer trials. You can't go to the pharmacy and buy it. Interferon, on the other hand, has been approved and private physicians can order interferon for patients for selected malignancies for which it has been proven to be effective.

The CHAIRMAN. All right—interferon is available. Interleukin 2 is being used for trials for the NIH and the Food and Drug Administration?

Dr. ERSHLER. Right. Yes. That's correct.

The CHAIRMAN. Thank you all very much. Senator Durenberger.

STATEMENT BY SENATOR DAVE DURENBERGER

Senator DURENBERGER. Mr. Chairman, thank you very much. I do have a couple of questions.

I finance in this country, or recommend the way we finance, some of the failures to do adequate research on aging. A lot of that is present in nursing homes in this country and hospitals and so forth, where we have the growing problem of the chronically ill.

The Chairman pointed out in his opening statement one thing that certainly bothered me. My question is going to be: Who is—what is setting the agenda now for research? Is it the availability of grants, or is it something else? I assume it's that. The Chairman pointed out, in his opening statement, that we spend in this country $50 billion or some very large number on Alzheimer's and a pittance on dementia. I guess that is because as a lot of older people in Minnesota have been telling me as I explore the issue, 10 years ago nobody knew what Alzheimer's was. In fact, some lady said, "I remember when I came out of the Mayo Clinic and they told me my husband had Alzheimer's I thought he was saying old timers disease." She said, "Now it has a name." And we recognize it so now all kinds of money is going into the research.

The first question is: Currently, what is setting the priorities for research? Is it the availability of grants from public agencies in this country, or is something else setting the priorities for research? Who wants to tackle that?

Dr. MAKINODAN. Well, I'm with the VA system, and funds to do aging research is very limited. There are close to 5 million veterans who are over 65 today. It is predicted that by the year 2000, this number will increase to somewhere around 9 million, or very close to 10 million. Yet, our research budget on aging and on the geriatric center is less than $30 million; there has been no increase over the past 4 years in spite of the fact that the number of veterans who are over 65 has been increasing at an astronomical rate. Thus, while there are competent scientists to do research in aging in the VA system, we just don't have funds to support them.

Senator DURENBERGER. And it strikes me there is a logic. We know it is a defined population. We know they're going to cost us an awful lot of money in the sense of our commitments to veterans. We know what average age they're at and you'd think we would have started a long time ago dealing with this.

What does it take? It just takes something from this committee, or somebody else?

Dr. MAKINODAN. Well, I hope this committee will have an impact in convincing the Appropriations Committee.

Dr. ERSHLER. I agree with Dr. Makinodan. I must say I wear two hats: I wear one with the VA in Madison; and one with the University which is directly contiguous. Actually, it's more like one big hat. I have approached both the NIH and the VA for funding and I have had funding from both. I must say, I think the VA does have a healthy commitment. They have limited resources, but they do have a healthy commitment for aging research.

I think with NIH, it is still difficult to obtain funding, even in these high priority areas. I know of many very capable investigators who are not receiving funding from either the VA or NIH for good aging research, because less than a third of the grants are funded and maybe less than that. I think I would implore the committee, really urge the committee, to go back and say that aging is a number one priority as our population ages and there are a lot of things we can do and a lot of room for improvement. There are things that can be done, but research must come first. We can really reduce, I think, in the long run, the budget that goes out for health care by doing basic and clinical research and preventive measures.

Senator DURENBERGER. Just a related question and I'll terminate because I wasn't able to get here earlier and I regret that and I know the Chairman's been here a long time.

Has your advice been asked yet as to where those of us would go who are interested in the value that aging research would bring, not only to healthier older people, but also to Federal budgets and private savings and a whole lot of other things? Where would we go as a Nation to get the best advice on where we ought to start and how we ought to set our priorities? Have you got some recommendations as to where we're going to get the best advice, if we were to make recommendations as to where to start, what should the priority be today, and how much of an investment ought we to put in?

Dr. MAKINODAN. I believe the Alliance for Aging Research will be a very good organization.

Senator DURENBERGER. Is that a group of people who do research now and want to get more money for their research, or what is it?

Dr. MAKINODAN. Perhaps, Dan Perry can come up here. Where is he?

Senator DURENBERGER. Begin with the Alliance.

Dr. MAKINODAN. Yes, because that organization has been coordinating the efforts of many research organizations with vested interest in aging research.

Senator DURENBERGER. You've been recommended as the best responder to the question, which is, where, if we are setting the priorities—did the Chairman cover all the bases with this witness list today, or are there other places we should be looking in this society to get advice on where to start and what to make a priority in our research.

Mr. PERRY. Senator, the witnesses that have testified before you today really represent some of the cream of the research community, not only in this country, but from other nations as well. You have heard what might be done in a very short term to intervene against some of these crippling and very expensive diseases.

Our organization, The Alliance for Aging Research, which combines scientific know-how, such as you heard this morning, with leaders of corporate America, senior executives from some of the major foundations in this country, and many Members of Congress who serve us as advisors. We have prepared an alternative budget for fiscal year 1989, measuring what is being done at the VA, the National Institute on Aging, the National Neurological Institute, the Arthritis Institute and even the Agriculture Department,

which we mentioned a bit earlier, which I know is an interest of the Chairman's.

Our organization is working to determine what could be spent rationally and responsibly, not just throwing dollars at it; what we might be able to do in the next few years if we had adequate resources. We have prepared that document; it has been introduced into the record this morning. I would be happy to share another copy with you, Senator. We will be officially releasing it in a press conference in the Capitol either Monday or Tuesday of next week. I think that will answer your questions.

Senator DURENBERGER. Thank you, Mr. Chairman, thank you very much for having this hearing.

The CHAIRMAN. Thank you, Senator. I don't know how near complete the spectrum that we've had as witnesses this morning is. I suspect it isn't bad for one morning. I am reassured by what Dan Perry has just said because it is our view that at this conference at George Washington University some—if not all—of the cream of the aging research is represented.

I think it's fair to say that when you're talking about immunology and nutrition and the use of the hormone estrogen to avoid osteoporosis problems in the elderly, we are not talking so much about spending money; we're talking about how we're going to save money. It comes through loud and clear to me, how we can invest something that will permit us to save money. I think Alzheimer's is a very good example. The range of costs for a year for taking care of the 2.5 million Alzheimer's victims that we've identified seems to be, from several witnesses, somewhere from $50 billion on up, perhaps as high as $90 billion. Yet we find if we total up all of the research that's being done on Alzheimer's, it's hard to get beyond $80 million or $90 million a year. So, it is just a very good acute example—acute—not just cute—of where more research dollars are needed.

Also, nutrition-wise, if we don't have the basic information, on the nutritional needs of age groups age 50 and beyond, we're missing a bet because that should be obtained and it should be obtained as accurately as possible and as completely as possible.

I want to thank all of you very much because, not just this panel, not just Dan Perry, but the other witness. I think that for 2½ hours, which is a very very short period of time, we've been given valuable insights into some of the worldwide efforts of medical research for the elderly. This hearing has shown that we're on the threshold of some very important findings to make the lives of the elderly much more comfortable and fruitful. As I said earlier, maybe there's hope for having fun after 80 or 85 years of age. I certainly hope so. I'm working hard to make sure that it happens because another generation and I'll be well into my middle and late 80's.

I want to thank you all very much and thank the other witnesses too.

The committee hearing record will be held open for 2 weeks. With that we adjourn.

[Whereupon, at 12:15 p.m., the committee was adjourned.]

APPENDIX

MATERIAL RELATED TO HEARING

Item 1

QUESTIONS FROM SENATOR GRASSLEY
MAY 11, 1988

QUESTIONS FOR GEORGE G. GLENNER

1. WHEN YOU SAY THAT YOU ARE OPTIMISTIC THAT, "IN THE FORESEEABLE FUTURE", WE WILL FIND A TREATMENT FOR ALZHEIMER'S RESEARCH, WHAT DO YOU MEAN? DO YOU MEAN PREVENTION AS OPPOSED TO CURE, OR DO YOU MEAN BOTH? AND WHAT KIND OF TIME SCHEDULE ARE WE TALKING ABOUT?

2. IN ORDER TO FIND THE SOLUTION TO ALZHEIMER'S DISEASE WHICH YOU HAVE SUGGESTED IS POSSIBLE, DO WE NEED AN INCREASE IN THE FINANCIAL SUPPORT WE ARE PRESENTLY PROVIDING, AND, IF SO, HOW MUCH ADDITIONAL SUPPORT ARE WE TALKING ABOUT?

3. IT IS APPARENT FROM YOUR STATEMENT THAT YOU ARE DEEPLY INVOLVED BOTH IN BIOMEDICAL RESEARCH ON ALZHEIMER'S DISEASE AND IN THE CARE OF INDIVIDUALS WITH THE DISEASE.

I WOULD LIKE TO ASK YOU A QUESTION ABOUT THE CARE OF THOSE WITH ALZHEIMER'S DISEASE.

WHEN THE SUBCOMMITTEE ON AGING OF THE LABOR COMMITTEE UNDER TOOK ITS PROJECT ON ALZHEIMER'S DISEASE IN THE 99TH CONGRESS, A NUMBER OF RESEARCHERS INVOLVED IN STUDYING HOW PEOPLE WITH ALZHEIMER'S WERE CARED FOR MAINTAINED THAT THE METHOD OF CARE AND TREATMENT MADE A DIFFERENCE IN THE WELL-BEING OF BOTH THE PERSON WITH THE DISEASE AND OF THE FAMILY.

YET WHEN WE TRIED TO GET SUPPORT FROM THE APPROPRIATIONS COMMITTEE FOR SOME OF THE PROVISIONS INCLUDED IN LEGISLATION INTRODUCED BY SENATOR METZENBAUM AND MYSELF WHICH WOULD HAVE SUPPORTED RESEARCH ON TREATMENT SETTINGS AND METHODS, WE FOUND THAT SUCH RESEARCH WAS CONSIDERED A WASTE OF TIME SINCE, "AFTER ALL, ONCE A PERSON HAS ALZHEIMER'S DISEASE, THEY'VE BECOME VEGETABLES AND THE CARE SETTING CAN'T REALLY MAKE MUCH DIFFERENCE".

DO YOU HAVE A VIEW ON THIS MATTER?

UNIVERSITY OF CALIFORNIA, SAN DIEGO

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DEPARTMENT OF PATHOLOGY, M-012
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GEORGE G. GLENNER, M.D.

June 14, 1988

The Honorable John Melcher
Senate Subcommittee on Aging
United States Senate
Senator Dirksen Building, Room G-41
Washington, D.C. 20510-6400

Attention: Ms. Holly Bode

Dear Holly:

The following are my answers to Senator Grassley's questions:

1. There is a short discussion on p. 43 of the California Alzheimer's Disease Task Force Report which I sent to Senator Melcher, on terms relating to "treatment" which I failed, unfortunately, to employ in my own talk. I am referring in my speech to both arrestive and prophylactic treatment. Therefore, I mean both preventing the onset as well as stopping the progress of the disease, but <u>not</u> reversing the damage already done. I see this by the turn of the century (2,000 AD, but I am a notoriously poor Nostradamus).

2. We definitely need an increase in funding in order to determine the cause and cure of Alzheimer's disease. At present we are funding $68 million compared to the cost of care of $48 billion or 0.14%. The ratio should be at <u>least</u> 1% of the cost of care or $680 million. Industry usually uses a figure of 3% of income or profits for R&D. As Senator Melcher said "we are not spending money but are saving it" (by supporting research).

3. With regard to the quotation on a person with Alzheimer's disease, it could not be more misguided, inappropriate or erroneous and smacks of total ignorance of care for Alzheimer's disease patients. First of all Alzheimer's patients during the greater course (two-thirds) of their disease of 5-20 years are not "vegetables", but are recent-memory impaired, physically active, feeling, agitated, confused and depressed human beings who progressively lose their ability to communicate verbally and to reason. It is only in the terminate phase of the disease that they may be bedridden and/or comatose. However, many of our patients at the Alzheimer's Family Center (AFC) die before ever being bedridden.

We have found that in a care setting such as the AFC, patients improve in communication and are happier and more responsive and return to their home psychologically much improved. This is because the stimulation, attention and TLC reduces the severe depression (often misdiagnosed as a psychiatric depression) all of them initially have as a result of their recent-memory loss. Thus both the patient and the caregiver are happier and more relaxed. The caregivers almost in unison tell us it(the Alzheimer's Family Center) "has saved our lives." The feeling of the patients can best be epitomized by a statement of one of our least coherent members, who after a bout of incontinence at the Center said clearly to our Staff after they had washed and redressed him: "With people like you God can take a holiday".

Since our average patient time at the AFC is 2-3 days per week this means that this respite period provides sufficient relief from the "36 hour" day demanded of the caregiver to prevent institutionalization of the patient and/or physical exhaustion of the caregiver. The disease produces isolation of the caregiver when friends and family no longer visit and produces a jailor-jailed syndrome since attempts to restrain the patient from wandering out of the house demands locked doors and constant surveillance. This is relieved by community-based respite care.

For the family we are giving surcease from emotional, physical and financial devastation. In giving these patients their dignity and a feeling of self-esteem and love, we are only giving them something all of us would wish in our final days, since all of us eventually will die.

Very sincerely yours,

George G. Glenner, M.D.
Professor of Pathology
Director, National Alzheimer's Disease
Brain Bank & Research

GGG/mz

Item 2

Mr. Daniel Perry
Executive Director
Alliance for Aging Research

Question: When we talk about aging research, we usually discuss funding levels. With the millions of dollars spent on federal funding research, how effectively do you feel that federal agencies disseminate the research results to policy makers, academic institutions and the public? What changes would you suggest to better disseminate the results of research funded by the federal government?

Alliance for Aging Research

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Daniel Perry

June 16, 1988

Honorable Larry Pressler
Senate Special Committee on Aging
SD-G41
Washington, DC 20510-6400

Dear Senator Pressler,

Thank you for your question regarding the communication and dissemination of research results in aging. The Alliance for Aging Research is grateful for your interest and support for scientific studies of human aging.

American scientific research is heavily subsidized by the federal government, as you have said. The principal means by which new research findings are communicated by the scientific community is through scientific journals, publications and symposia. A rigorous review process for submitted articles makes for a rather slow and conservative means of dissemination new information. However the benefits of accuracy and verifiability, which are more nearly assured by scrupulous peer review, most likely out-weight the system's faults. While this provides for a sound means of disseminating research results within the scientific/academic communities, it is less effective for communication with policymakers and with the public.

Information about research results that passes from Executive Branch agencies to Congressional policymakers is heavily influenced by inter-governmental competition for funds and budget considerations. In contrast to information that is disseminated in the scientific journals as stated above, reports on research that come from federal agencies supporting research tend to be summary in nature. Depending upon the budget and fiscal climate, these reports tend to confirm either that "the glass is half-full or otherwise half-empty." That is, summaries from federal agencies can suggest either that the pace of research is about what is should be, or that a greater investment could lead to breakthroughs toward improvements in geriatric health in a shorter period of time. The considerations in such summaries are governed

more by political, rather than scientific or public health considerations. I do not wish to sound cynical in this regard, Senator. The reports and testimony given by the National Institutes of Health and other federal agencies to the Congress are no better or worse that those provided by other agencies of the U.S. government. Their contents are framed by issues that go beyond the communication of research results.

It is where the public is concerned that I believe effective communication about aging research and its role in national science policies is most lacking. The news that the public receives in this area can be roughly divided into two categories: 1) that which discourages belief that current research will have any real effect on aging, and 2) articles in some consumer-oriented and sensationalist journals that suggests that food-additives and the like supposedly can cure disease and retard aging. There have been some laudable exceptions to this pattern. Recently ABC Television produced a one-hour segment of the 20/20 program titled "Slowing the Clock." It was an excellent documentary showing examples of far-reaching aging research in a responsible and informative fashion. There is a need for more journalistic attention and treatment of the promise of aging research in programming and in the print media.

One goal of the Alliance for Aging Research is to improve the communication of information about this research among scientists, policymakers and the general public. As you know, our organization is barely 18 months old and there is much to do to build better communications and hence a broader consensus behind advanced scientific research into human aging. The Alliance is proud to have you as a member of our Congressional Advisory Board. I would be glad to explore further with you and with your staff innovations in the exchange of information about research in aging that might improve the situation I have described here.

In addition to my own views I have solicited a response to your question from Dr. Arthur K. Balin of the Rockefeller University in New York City. In addition to his academic and research activities, Dr. Balin is President of the American Aging Association, a group of scientists in the field of aging. Dr. Balin is also known for actively contributing to regular exchanges of research findings among scientists in key disciplines. With your permission, I would like to include Dr. Balin's response to your question along with my own.

Sincerely,

Dan Perry

Daniel Perry
Executive Director

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE • NEW YORK, NEW YORK 10021-6399

ARTHUR K. BALIN, M.D., PH.D.
Diplomate, American Board of Dermatology
Diplomate, American Board of Internal Medicine
Special Competence, Dermatopathology,
American Boards of Pathology and Dermatology

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June 10, 1988

Senator Larry Pressler
SR-470A Russell Senate Office Bldg.
Washington, DC 20510

Dear Senator Pressler:

You asked whether the NIH could be doing more to inform the public about the results of the research that is being performed. The answer is a resounding yes. The public needs to be informed about the benefits that have accrued from research sponsored by government funding of the National Institute of Health.

We are shooting ourselves in the foot. Or worse. Many in our society finish high school, a lesser number complete college, and relatively speaking very few go on to complete doctorate degrees in medicine and in the biomedical sciences. From a societal standpoint, only a handful of individuals hold advanced professional degrees and are engaged in biomedical or scientific research. These individuals have been culled from each community and number just a few thousand out of the 265 million people in our country. They represent a national resource, a treasure of inestimable value to our society because they perform the scientific research, invention, and discovery that is required for understanding and improving the human condition.

The creativeness of scientific researchers has led in a mere 100 years from horse and buggy days to men working on the moon; and in the medical field from death at a young age from common infections such as might be obtained from a cut or scrape, or pneumococcal pneumonia, to a cure of these problems through modern antibiotics. Or from a situation in which an injury to the leg required a few shots of whiskey as crude amputation was performed and bleeding controlled with a hot branding iron to the present day when a severe injury can be repaired using microvascular surgery and modern methods of anesthesia. This transformation has come about because of the education of our population, the increasing knowledge in mathematics and in the sciences and the creative ingenuity, genius and hard work of our most talented medical and scientific researchers. Unfortunately, these scientific and medical transformations are taken for granted by our population.

Why do I say the NIH should do more to educate and inform the public about the medical research it has fostered and sponsored? If people are reminded of the benefits and improvements in their life that scientific research has brought about and if they could be made aware of the tremendous waste of our most precious resource (the educated creative scientific mind) a groundswell of indignation would arise to restructure our national priorities and remedy this situation. It takes over 25 years to educate the most fledgling

physician or scientist. At present, only 20% of the grant requests that are submitted to the NIH and that are deemed scientifically acceptable and worthwhile to be performed are being funded by the NIH. This is about 7,000 grants per year. This means that in our society of 265 million people only 7,000 principal investigators are supported to do creative scientific medical research. This is absurd. This is crazy. This is a waste of our most valuable resource. Every one of the grants which are deemed scientifically worthwhile to be pursued should be funded. At present, this would mean approximately 35,000 grants.

Research is the lifeblood of growth, evolution, and transformation of our society. What happens to the 28,000 other principal investigators who have 25 or 30 years of education and whose scientific research inquiry is deemed valid and important to pursue yet there is no money to fund their research projects? Some of the scientists hang on and reapply. Some have to disband their research groups that have been built up over many years. Even if a new application is eventually approved it takes years to re-establish the same level of expertise that was present at the time that funding was interrupted. An increasing number of disillusioned scientists are leaving scientific research for other careers that have a more secure financial base and from which they can be assured of supporting their families. Each scientist lost takes years to recover and they are not easily replaceable. Each one has completed high school, college, and medical school or graduate school with an M.D. or Ph.D. degree. They are already the educational cream of our society and should, after all this education and selection and training, we be only utilizing the intelligence of 20% of our scientists? By putting all 100% to work in scientific research we would immediately have an additional five generations of scientists; the most capable, respectable, educated and trained individuals in the history of mankind to work on current medical and scientific problems. What an efficient use of our already available manpower. Can there be any doubt that transformation in our society will be wrought as the scientific discoveries of five additional generations of fully trained scientists come to fruition?

How are we going to attain a world without smog, pollution and acid rain? How are we going to attain a long and healthy life without illness and disease? How are we going to attain adequate nutrition and food for the entire world's population? Scientific and medical research will provide the knowledge, the basis, and finally the discoveries that will lead to achieving each of these goals. The imagination of the public should be tweaked by the possibilities that scientific research may develop. Yet we should be cautious and not mislead the public. It seems to me that it would be prudent to focus on what has already been accomplished and to show how our life has been transformed by past discoveries. While, it is easy to imagine what the future might hold if we invest our resources in biomedical research, as scientists we can't predict specific achievements.

In my opinion, this our most important national priority. Scientific and medical research represents the way to improve the human condition and alleviate suffering in our society. A public mobilized and supportive of the efforts of research scientists would greatly speed the attainment of these desired objectives. What would the consequences of a five fold increase in the number of funded grants mean. The immediate effect irrespective of any discoveries made would be markedly stimulatory to our economy. Grant money is distributed in relatively small amounts to institutions throughout the country. Generally, part of the money is used to support the salaries of investigators, laboratory technicians, and research assistants. The remainder of the money is used for scientific equipment and supplies and thus is redistributed back into our economy to support thousands of sales people and the companies that they represent. Finally, the profits that the companies make are distributed back to their investors. So the immediate consequences would be a stimulation to the economy. With a five fold increase in the number of researchers, a second consequence would be to greatly stimulate the number and education of new students pursuing scientific research. This would enable an eventual acceleration in the

level of research presumably at a time when our society has realized that this is a wise and inexpensive investment in terms of the return to the society. Finally, the research itself is has a very high probability of enormous economic payoff. Just consider the enormous percentage of our gross national product that has been influenced or enabled by medical and scientific advances . Almost everything in our society is influenced in some way by these discoveries. Thus, while specific advances cannot be promised, the track record indicates that they will certainly accrue to our civilization. Indeed, with the specter of diseases such as AIDS looming on the horizon, it is conceivable that the continued existence of our civilization depends on scientific and medical research.

Some might say that there seems to be sufficient profit in medical research that we should simply allow private companies to undertake it. This is a dangerous and short-sided view. Benefits that accrue from the federal government supporting medical and scientific research include the education of the next generation of scientists and the wide dissemination of the discoveries made. Basic scientific research has a very long lead time until the basic discoveries are translated into practical utility. This has been one of the major problems in educating the public regarding what benefit they are getting from the research that is being performed. When basic biomedical research is performed in a company the discoveries as well as the intermediary steps may remain proprietary information. This can greatly inhibit the advancement of science because it prevents other scientists from benefitting from the knowledge of the unfruitful steps which were encountered during the course of investigation. In addition, it makes it much more difficult for other scientists to make major advances by making connections between published work of one scientist and their own course of investigation. Although scientific research by private companies is a benefit, it should not substitute for government funded research.

Now, to the question of what can and should the NIH do with respect to the education of federal policy makers, academic leaders, and the general public. By and large, the academic community has access to the results of scientific discoveries and research performed through the scientific journals. I am not certain as to the extent that the federal policy makers are briefed by the NIH regarding past achievements and current research, so I cannot comment on the adequacy of briefing for federal policy makers. With respect to the public, there has been very little effort to inform and educate the public regarding the benefits of the scientific discoveries that have been performed with governmental funds through the NIH. This is a deficiency which should clearly be remedied since enthusiastic public support is needed to encourage federal authorities to fund all approved and submitted grants.

How should education of the public be implemented? First, a decision should be made that it is the responsibility of the NIH to inform and educate the public regarding the value of scientific research. As far as I can tell, there is no mandate for anyone to take responsibility regarding educating the public. This education should take the form of enumerating the benefits that have accrued from federal investment in medical and scientific research and can be a litany of achievements over the past years of federal support. It could easily include discoveries made by others working without federal support since much of the knowledge base that enable other discoveries to be made results from NIH supported basic biomedical research. I think a carefully designed informational and educational program that would inform the public about the benefits of NIH-sponsored biomedical research would be useful in generating public enthusiasm for this support. I would propose that the NIH be directly allowed to solicit private contributions which would be tax deductible to augment its research budget. In addition, I would propose that the NIH be specifically allowed to encourage people to communicate with their elected representatives regarding their degree of interest, enthusiasm, and support for biomedical research.

I have not addressed myself specifically to biomedical aging research because the accomplishments in this field are still in their infancy. Aging research has been particularly underfunded considering the magnitude and immediacy of the subject probably because it tends to be difficult to perform and requires a long-term approach. Many of the aging grants fall in the four-fifths of submitted grants which are approved but not funded.

Sincerely,

Arthur K Balin, MD

Arthur K. Balin, M.D., Ph.D.

Assistant Professor and Associate Physician
The Rockefeller University

President, American Aging Association

Item 3

American
Psychiatric
Association

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May 5, 1988

The Honorable John Melcher
Chairman
Senate Special Committee on Aging
G41 Dirksen Senate Office Building
Washington, DC 20510

Dear Senator Melcher:

The American Psychiatric Association, a medical specialty society representing more than 34,000 psychiatrists nationwide, is pleased to submit this statement highlighting psychiatric advances in aging research. APA commends the Senate Special Committee on Aging for focusing on "Biomedical Advances in Aging Research".

As you well know, the Institute of Medicine of the National Academy of Science has stated that the personal and social costs of mental illness and substance abuse disorders are comparable to those for heart disease and cancer. Despite the fact that the costs of these disorders amount to approximately $1,000 per year for every man, woman and child in the U.S., the federal commitment to research funds to combat these disorders in FY 1988 is approximately $1.80 per person.

Even with the de minimus investment in research, advances have been made in many areas including:

- o understanding the scope of mental disorders in the elderly,
- o understanding the pathophysiology of mental disorders,
- o treating mental disorders in the elderly
- o using new techniques to diagnose these disorders,
- o understanding the impact of mental disorders on the course of physical illness,
- o and tracing the physiological stages of these disorders.

Highlights of these advances are discussed below:

Etiology and Pathophysiology of Certain Mental Disorders

The search for the etiology of mental disorders has resulted in new discoveries about their pathophysiology. These advances are noted below.

- o Schizophrenia--National Institute of Mental Health (NIMH) intramural and extramural researchers have improved our recognition of the existence of a late onset form of schizophrenia, included in the U.S. official nomenclature in 1987. By specifically diagnosing such a disorder, patients with this form of "pseudodementia" will not be misdiagnosed as Alzheimer Disease (AD) patients.

- o Alzheimer's Disease--Many areas of basic research have helped to clarify and elucidate the potential etiology of Alzheimer's disease. First, research identifying the significantly increased frequency of Down's syndrome in families with an Alzheimer's patient helped to focus the search for a genetic marker onto Chromosome 21 (Heston, Minnesota). Second, a team of researchers at Johns Hopkins identified the Nucleus Basilis of Meynert (nBM) as one of the earliest lesion sites in Alzheimer's Disease (Coyle et. al., Johns Hopkins). This discovery changed the view of AD as primiarily a cortical disorder. These same researchers also found nBM to be rich in neurons producing acetylycholine--the neurotransmitter diminished in Alzheimer's disease. Third, the discovery of the fact that A-68 is a protein that appears to be found in quantity in the brains of AD patients (Davies, Albert Einstein). If the finding

is reproducable new insights into the cause of the disorder could occur. Fourth, scientists have been able to rule out aluminum as a causative agent in the treatment of AD.

- o Depression-Depression wears many masks in the elderly. It may appear as pseudodementia (Reisberg, NYU) and may be an excess diasability factor in Alzheimer's Disease (Reifler and Larson, University of Washington). The methodolgy for conducting clinical trials of antidepressants in nursing homes has been developed (Katz and Simpson).

Research on Diagnostic Techniques

In recent years, Positron Emission Tomography (PET), has made it possible to identify metabolic differences in specific portions of the brains of those suffering from schizophrenia or manic depression from those of normal controls. Brain imaging studies at NYU are increasing our understanding of the role and limits of the CT scans and PET scans in the diagnosis of AD. Certain changes noted in the PET scans of Alzheimer's patients are demonstrated later on PET scans than on CT scans, suggesting that a significant degree of brain atrophy can occur before pathological metabolic findings emerge on PET scans in these patients. Computer analyzed electroencephlography (EEG) studies show some potential for differentiating dementia of the Alzheimer's type from multi-infarct dementia (Leuchter, UCLA). Research has also demonstrated an improved understanding of the diagnostic yield or accuracy of different groups of clinical tests in the clinical diagnosis of Alzheimer's disease. Neurophsychological testing has also assisted us to differentiate Korsekoff's dementia from Alzheimer's type dementia.

Treatment Research

Researchers have explored a wide range of psychopharamacologic and other treatment alternatives. Since more drugs are used by the elderly than any other group, this research is obviously critical. Researchers also have improved our understanding of the pharmacokinetics of bensodiazepines in the elderly. Through research on tricyclics the pharmacologic management of depression has greatly improved. Attempts at improving memory function through use of drugs have resulted in minor improvements for limited duration in patients with AD.

"Excess disability" has been identified in AD patients where concomitant symptoms of depression and delusions which comprise clinical subtypes of AD compound the dementia of these patients, causing more impairment than would be the case in dementia alone. These excess disability states can be lifted by somatic and nonsomatic treatments.

Summary

In sum, the science of understanding mental illness has changed greatly. New advances in the diagnosis, treatment and understanding of these illnesses will likely produce major additional research breakthroughs in the future. As noted in the Report to Congress on the Decade of the Brain, 1988: "We are poised for neuroscience breakthroughs in the 1980s that will generate clinical successes during the 21st century...The most important benefit would be in the improved quality of life for patients and their families."

Attached for the record is the budget alternative to the President's FY 1989 research and research training budget for the Alchohol, Drug, Abuse and Mental Health Administration. In addition, the second brochure details for you descriptive information on Alzheimer's Disease.

Sincerely,

Jay Cutler

Jay M. Cutler
Special Counsel and Director
Division of Government Relations

Item 4

IN: Handbook of Neurochemistry
4th edition
(Siegel, Albers, Agranoff & Katzman ,eds)
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AGING

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Introduction. Twenty-nine million Americans are 65 years of age or older. This represents about 11% of the total population (Fig. 1). Americans aged 85 and older are the fastest growing segment of the population, and this group, which is the most critical group in terms of health and social services, is expected to triple by the year 2020. These findings indicate that new emphasis must be placed on aging research to accomodate a growing aged population. In addition to the obvious human costs of aging, the elderly are also a financial concern, representing one-third of the nation's health costs. Fortunately, aging research is expanding and progress is being made to elucidate the mechanisms that underlie the aging process.

Most studies on aging emphasize age-related functional losses. During the past decade, major deficits have been reported in such clinically relevant variables as hearing, vision, olfaction, glucose tolerance, immune response, endocrine function, sympathetic nervous system activity, learning and memory. Losses are reported to occur in a number of central nervous system metabolic functions which suggests that aging leads to a progressive decline in brain and body function.

Until recently, individual variability with respect to physiological or behavioral measures has been neglected. In nearly all aging studies, heterogeneity within the aged population increases. Some elderly subjects fall within the normal range for adult subjects (e.g. age sucessfully), while others show critical losses. Deviations may be due to illnesses or environmental factors rather than aging per se. In addition to variations in hereditary, different lifestyles can either compromise or enhance vitality. Thus, heterogeneity may be an inherent characteristic of the aging process.

Some individuals may age more successfully than others. The study of successful versus usual aging [1] introduces new and exciting challenges to the neurochemist. The characteristics of successful aging need to be defined. Functions that do not change may be just as important as those that do. Much of the recent neurochemical literature suggests that more functions and systems are maintained than predicted from the current dogma that aging is associated with an inevitable decline until death. Some individuals may show fewer deficits and/or possess better adaptive mechanisms which compensate for losses in order to preserve key functions. In this chapter, the issue of lost versus preserved function, at a cellular and molecular level, will be examined. It is appropriate to start the discussion with a definition of aging.

Aging is an irreversible process, that begins at maturity and is characterized by increasing deviations from an ideal functional state. Aging is generally associated with an exponential rise in the presence of pathological changes; however, it is not a series of diseases whose cumulative effect leads to death. Increasing age causes predictable chronological losses of certain biological functions. Proper biological function depends on a fine balance of neural and endocrine signals which sense internal and external environmental fluctuations and regulate cellular functions accordingly. The decline in adaptive or compensatory mechanisms with

aging may predispose the individual to various diseases, compromise vitality and shorten lifespan.

Aging research presents challenges beyond those of most disciplines in the neurosciences. Many changes in the central nervous system may not be primary to the aging process. Nerve cell degeneration, for example, can occur secondarily to deficits in the aging cardiovascular system. The critical challenge is to design experiments that identify the primary versus secondary events. Another issue is to determine how much of a deficit is required before dynamic cell functions are compromised. Often percent declines do not reflect physiological significance.

Neuron loss is not an inevitable consequence of aging, although it can occur. There are several noticeable gross changes in the aged human brain, such as a decline in brain volume and weight, enlargement of the ventricles, and narrowing of the gyri and sulci. Surprisingly, the total number of neurons, neuronal density and percentage of cell area in the cerebral cortex are unchanged with normal aging [2]. Large neurons appear to atrophy with a consequent increase in the number of small neurons (Fig. 2A). After 55 years of age, there is a progressive increase in the number of atrophied neurons although there is wide variation within the population (Fig. 2B). The number of glial cells also increase with aging (Fig. 2C), which reduces the neuron to glial cell ratio.

In contrast to cerebral cortex, the substantia nigra shows a progressive loss of dopaminergic neurons, beginning at approximately 30 years of age (Fig. 3; [3]). Thus aging clearly does not affect all brain areas equally [4]. It should be noted that studies on neuronal density should be scrutinized closely since earlier studies may not have used adequate volumetric methodologies and some of the subjects may have had undetected diseases.

In aged rodents, there is suprisingly little evidence of major cell loss late in life. In the rat substantia nigra, cell loss is not as prominent as has been reported in man [for review see 5]. Cell loss is less than 20% whereas in man it can exceed 60%. Recent studies suggest that the nigra cell loss may be related to environmental factors which indicates that the rodent data may be a more accurate representation of age-related cell loss.

In the rodent hippocampus, neuronal loss does not exceed 20% and synaptic density is also maintained. It appears that those specific subfields of the hippocampus (e.g. CA1 and CA3) which lose neurons during aging are also selectively vulnerable to metabolic encephalopathies (e.g. ischemia, hypoxia, hypoglycemia). This suggests that selected neurons are generally more susceptible to both aging and pathology. Theories of aging in the central nervous system need to account for selective vulnerability.

Synaptic and dendritic plasticity may compensate for some cell loss in the aged brain. Some brain regions show very minor, whereas others show major, neuronal losses. Despite these neuronal losses, however, the functional capacity of central nervous system circuits may be preserved beyond that predicted from cell loss alone. It has been suggested that the loss of neurons triggers the surviving cells to sprout and replace lost connections. This is consistent with studies of reactive synaptogenesis in the injured aged brain [6]. In brain regions that show partial neuronal loss, dendritic arbors actually continue to grow between middle and old age (Fig 4A; [for discussion see 7]). Thus, during aging, compensation mechanisms of growth and remodeling, such as dendritic hypertrophy and synaptic growth, may be part of the lifelong program to maintain and adapt brain function. Only in very old age in man does the dendritic tree appear to regress to that of mature adults (Fig. 4B and C).

Synaptic transmission may show deficits in select parameters but adaptive mechanisms may in some cases maintain function. In the aging brain it appears that much of the essential circuitry is present and some of the functional losses may be compensated for by intrinsic mechanisms of synaptic plasticity. How then do these circuitries function at the level of the synapse? Studies on synaptic transmission may provide a focal point for neurochemical, electrophysiological and behavioral studies.

In the central nervous system, acetylcholine is quantitatively a minor neurotransmitter; however, it is thought to play a key role in intellectual activity, including memory. Treatment of young subjects with scopolamine, an acetylcholine antagonist, produces memory deficits similar to those observed in elderly subjects. In the central nervous system, deficits in various cholinergic markers suggest a decline in cholinergic synaptic transmission. *In vivo* and *in vitro* acetylcholine

synthesis, release and choline uptake are depressed by aging despite no changes in either choline or acetylcholine content [for review see 8]. Acetylcholine metabolism is subject to rapid post-mortem changes so that the most popular post-mortem index of cholinergic neuron integrity is choline acetyltransferase activity. Age-related differences in choline acetyltransferase and acetylcholinesterase activities are inconsistent, although these enzymes markedly decline in Alzheimer's disease. With aging, muscarinic receptor number seems to decline while receptor affinity is unaltered. The response of hippocampal pyramidal cells to iontophoretic acetylcholine decreases with age [for review see 9]. It would be expected that cholinergic transmission would be diminished, but direct electrophysiological evidence has not yet been reported. It is possible that various regulatory steps may compensate for loss of specific measures.

Pre- and post-synaptic dopamine metabolism is selectively altered by aging. Both the levels of dopamine and the number of midbrain dopamine-containing neurons decline (-50%) but not until very old age. This occurs even in the absence of neurological disease [for review see 5]. The density of dopamine D2 receptors (autoreceptor for feedback inhibition of dopamine release) decrease (-40%) while D1 receptors (the receptors linked to adenylate cyclase activity) are either increased (humans) or unchanged (rodents). The most consistent age-related decline is in striatal dopamine metabolism (e.g. content, synthesis, receptor binding). It has been suggested that the loss of D2 receptors is related to reduced presynaptic input while the D1 receptor represents modest supersensitivity. Similar changes have been reported in rodents although the losses are comparatively minor.

Norepinephrine shares several enzymes of synthesis and catabolism with dopamine. Thus, many of the age-related changes in the dopamine system also occur in with norepinephrine. Depressed tyrosine hydroxylase activity decreases both norepinephrine and dopamine synthesis. The effect of age on serotonergic neurons has been studied less extensively than catecholamines, and the resulting reports are inconsistent. Relatively detailed studies on a variety of neurotransmitter-related parameters have been done on a variety of brain regions [for review see 4].

A limitation of neurochemical measures of transmitter-related parameters is that they predict but do not provide a direct index of function. It is possible that deficits in one or more aspects of neurotransmission may be compensated by changes in others. Studies on the function, structure and chemistry of synaptic transmission at the neuromuscular junction are particularly illustrative in this respect.

Synaptic transmission at the rat neuromuscular junction appears to be maintained over a wide range of stimulus conditions, perhaps through an adaptive integration of various aspects of cholinergic metabolism. Between 10 and 28 months of age, the average number of nerve terminals per end plate increases by 34% (Fig. 5A). Resting acetylcholine efflux is greater in old rats (3.0 pmol/min) when compared to young rats (2.0 pmol/min); this is probably related to the greater number of terminals. At rest, endogenous choline levels are unchanged; however, choline uptake is increased (+28%).

Total acetylcholine release evoked by stimulation (1-20 Hz) is similar in both young and old animals (Fig. 5B and C; [10]) even though endogenous acetylcholine levels are reduced (-34%). The lower acetylcholine concentrations appear due to enhanced leakage of ACh from nerve terminals. To compensate for lower pools, choline incorporation into acetylcholine is faster in aged rats (i.e., time to half-maximal steady state is 2 min at 10 months of age compared 0.6 min by 28 months). There are no changes in choline acetyltransferase activity [10]. Thus, due to a series of integrated adaptations, neuromuscular synaptic transmission over a physiologically broad range of stimulus conditions, can be retained with aging although it does fatigue more readily upon higher stimulation rates [11].

In the central nervous system, there are similar situations where adaptive mechanisms maintain synaptic transmission. Excitatory amino acids, such as glutamate, are the major neurotransmitters for excitatory pathways in the central nervous system. The role of excitatory amino acids in the aged brain is critical for normal function, as well as certain mechanisms of plasticity, such as long term potentiation. A subtype of excitatory amino acid receptor, the N-methyl-D-aspartate (NMDA) receptor, appears necessary for the development of long term potentiation. Long term potentiation is maintained in aged rodent brain although NMDA receptor binding declines [12].

In the aged brain, synaptic transmission actually appears to be enhanced in some pathways. The cortical input to the dentate gyrus in the aged rat appears to be potentiated even though there is modest cell loss within this circuit. It may be that increased transmitter release is due to additional terminals, enlargement of existing ones, more receptors or other mechanisms. Part of the enhancement appears to be due to an increased electronic coupling between target cells which makes it easier to fire more neurons to the same synaptic input [13].

Many issues remain unresolved in the study of synaptic transmission in the aged central nervous system. How much loss is needed before the aged individual is actually compromised? What pathways are most affected and which have preserved function? Partial neuronal loss may be compensated for by sprouting, adaptive increases in receptor number or other mechanisms. Decreased transmitter release may be inconsequential during basal activity but may be inadequate during periods of peak activity. Since neurotransmitter systems act in concert it is possible that deficits in one transmitter may be compensated for by changes in another but a decline in two interdependent transmitter systems may produce more than an additive decline. The current data suggests that age-related alterations need to be examined regionally, as well as according to cell type and transmitter systems. Newer experimental designs that include neurochemical, immunocytochemical and electrophysiological approaches may make this type of integrative analysis a very promising and exciting area.

Calcium homeostasis in the aged nervous system may be a fundamental mechanism regulating age-related changes. The regulation of calcium fluxes and its compartmentalization is essential to pre-synaptic (e.g., transmitter release), as well as post-synaptic events (e.g., excitability and second messenger responses). Calcium homeostasis, in different brain compartments (e.g. pre- and post-synaptic), may respond differently to aging. Cytosolic free calcium, which is the physiologically active pool of calcium, is only 1/10,000th of total neuronal calcium. Thus, alterations in the intracellular/extracellular calcium ratio could produce deleterious changes in cell function. Alterations in calcium homeostasis may influence a number of components which include, but are not restricted to, receptor mobility, the coupling of receptors with enzymes involved in phosphoinositol hydrolysis, the function of GTP-binding proteins, calcium transport systems, calcium binding proteins and calcium activated proteases ([or review see 14]. For example, the brain contains an abundance of calcium-activated proteases (e.g., calpain) which when either under- or over-activated can contribute to cellular damage. Calpain is present in high concentrations in selectively vulnerable neurons and also correlates with longevity [15]. In hippocampal brain slices from aged rats, repetitive stimulation appears to be associated with a prolonged calcium-dependent potassium-mediated after-hyperpolarization [for discussion see 14]. These data indirectly suggest that in aged rat hippocampal neurons cytosolic free calcium is increased. Cytosolic free calcium, however, has not been measured directly in the aged brain. However in peripheral tissues (e.g. fibroblasts and lymphocytes), aging appears to decrease cytosolic free calcium concentrations (Fig. 6; [16]). In view of calcium's regulatory mechanism, as well as its role in cell death, further studies need to be done.

Brain Energy Metabolism May be Preserved During Aging in Healthy Individuals. Normal brain function depends critically on the ability of its neurons and glia to synthesize high energy intermediates. Cerebral energy metabolism such as cerebral blood flow, cerebral metabolic rate for oxygen and cerebral metabolic rate for glucose have been examined in animals and human subjects of different ages. In aged rats, which have only few age-related neuropathological changes, there are only slight declines in energy metabolism and these changes are confined to sensory related areas.

Positron emission tomography (PET) is a non-invasive technique that estimates local rates of glucose metabolism in man. After ^{18}F-2-fluoro-2-deoxy-D-glucose is phosphorylated it accumulates in the central nervous system in proportion to rates of glucose utilization. Early PET scanning studies suggested that cerebral metabolic rate and cerebral blood flow were reduced overall, or at least in some brain regions. However these changes may have been due to inclusion of elderly subjects with various diseases in these studies. In a more detailed study [17], brain oxidative metabolism was measured in 40 healthy subjects (aged 21 to 83 years) selected for excellent cognitive ability and an absence of diseases that could interfere with cerebral function. In 25 brain regions, brain oxidative metabolism does not change significantly with age when

measured under conditions of reduced auditory and visual stimulation (Fig. 7). In elderly subjects resting cerebral metabolism shows an increased coefficient of variation which implies heterogeneity in this population. No significant relationship could be found between resting cerebral metabolism and intelligence. There was no correlation between blood pressure and age in these subjects although a significant positive correlation exists in the general population. These data underscore the importance of studying healthy subjects rather than using a representative sample of the general population. Thus a decline in oxidative cerebral metabolism is not an inevitable consequence of aging.

Neuropathological examination reveals that aging is characterized by the appearance of abnormal protein structures. While many functions are maintained pathology does arise. For examples, structures called neuritic or senile plaques can accumulate in the neuropile in brain regions, such as the frontal cortex or hippocampus. These plaques (about 20-50 microns in diameter) consist of enlarged axonal and dendritic processes which appear to sprout and then degenerate. In many cases, the degenerating neurities surround a core of extracellular proteinaceous filaments called ß amyloid. Senile plaques are found in the brain of man, primates and several other species such as dogs and polar bears but not in rats. They accumlulate with age and are present in even greater abundance in Alzheimer's disease.

Amyloid is an insoluble 4 kD protein with a high degree of a ß pleated sheet structure. The gene for the ß amyloid protein is on chromosome 21. Synthetic oligonucleotides based on the 4kD ß protein have been used to isolate the complementary deoxyribonucleic acid (cDNA) which encodes for the human ß amyloid protein. The amyloid gene is transcribed in brain of man and other species and surprisingly is also transcribed in almost all human tissues (e.g. kidney, heart, spleen, thymus but not liver). Genetic mapping studies show that families with an inherited form of Alzheimer's disease have an abnormal gene that is located on chromosome 21. It appears that the amyloid gene is in the same region of the chromosome as the familial Alzheimer gene; however, it is unclear whether the amyloid gene, or another closely associated gene product leads to Alzheimer's disease [for discussion see 18]. The ß amyloid protein is preferentially expressed in large pyramidal neurons of layers three and four of the prefrontal cortex and in CA1 hippocampal neurons that are involved in degeneration in Alzheimer's disease. Apparently some neuronal populations have a biochemical predilictiion for age-related pathologies although not all neural groups with high amyloid levels are involved in the pathological accumulation of amyloid. The normal function of amyloid is unknown. Beta-amyloid is derived from a large precursor protein which may have other functions. Isolation of a full length cDNA indicates an open reading frame of 695 amino acids which contains the shorter ß amyloid protein of 42 amino acids near its carboxy terminus. There are some indications that amyloid is contained within a membrane receptor protein.

With advancing age, there is also an increase in intraneuronal inclusions known as neurofibrillary tangles. Ultrastructurally neurofibrillary tangles are composed primarily of relatively insoluble proteins that assume a paired helical conformation. Although these structures are found in normal aged brain, they increase in number during the ninth and tenth decades of life. These structures are more commonly associated with the neuropathological diagnosis of Alzheimer's disease. Tangles are frequently located in the neuronal perikaryon and may enter the axon hillock or proximal dendrite. They are also found in axon terminals where they contribute to the neuritic component of senile or neuritic plaques.

The role of senile plaques and neurofibrillary tangles in aging is unknown. The progressive accumulation of plaques and tangles associated with areas of specific neuron loss is diagnostic of a brain with Alzheimer's disease. Some have argued that Alzheimer's disease in fact is a form of accelerated aging though this remains open to debate.

Lipofuscin is an autofluorescent lipoidal pigment which is one of the most common features of aging in neurons. This product is considered to be formed from undegradable waste products that are derived from partially degraded membranes and other cell components [for review see 19]. Lipofuscin accumulates in the axon hillock where it could interfere with the transport of materials within the axon. Certain neuronal groups within the motor system are especially prone to

accumulate lipofuscin, including the larger pyramidal cells of the cerebral cortex, the anterior horn cells of the spinal cord and the Purkinje cells. Lipofuscin accumulates as a linear function of age but it does not appear to correlate with the presence or extent of dementia or with other clinical features of disease.

At a behavioral level, function in the elderly is either adequate, inadequate or even improved depending on the task and the individual. The proper integration of the brain's chemistry must ultimately be expressed as behavior. A detailed discussion of age-related changes in behavior is beyond the scope of this chapter [for discussion see 1]; but some general points should be emphasized. Elderly people perform well on tasks in which they can rely on well-established skills and knowledge. Word finding difficulties are seldom observed in normal aging and in fact elderly subjects perform better than young subjects on certain tasks using verbal abilities. Elderly subjects do not perform as well as young individuals on timed tests of cognition and behavior. However, when aged individuals are given further time to respond they perform as well as young subjects; this may also be due to lack of recent practice by elderly subjects. After training, there is a substantial and retained improvement among individuals who were previously scored as cognitively impaired. In most studies there is variabilty within groups. Some elderly subjects show no or minimal cognitive losses when compared to younger counterparts.

Heterogeneity in learning ability has also been observed in rodent behavioral studies. For example, aged (21-23 months) rats were tested for their ability to find a hidden underwater platform in a circular tank that is placed in a room with extra-maze cues (e.g., windows, lamps, etc.). Out of a group of 75 aged rats, only 24 rats had impaired performance in the Morris water maze whereas the others did not (Fig.8; [20]). In animals studies, there have been various reports of age-related losses in behavior as well as no changes [for review see 9]. In aging behavioral studies, it is essential that deficits in the animal's motivation, motor abilities and sensory capacity, are not misinterpreted for deficits in learning and memory. For example, visual or olfactory impairments may be misinterpreted as learning difficulties in a task that requires searching for objects or food.

Several prominant theories of aging exist but these may be less applicable to the central nervous system. Many theories of aging have been developed based upon observations in other tissues and cell types [for review see 21] and then applied to the central nervous system. In general, theories of aging appear to have limited applicablity to the central nervous system. This can be illustrated by discussing three popular theories of aging. *In vitro*, many types of normal diploid cells (e.g, cultured fibroblasts) have a limited replicative life span (e.g., the Hayflick phenomena). How this theory applies to brain is unclear, since neurons are postmitotic and glial cells divide infrequently. Another theory of aging suggests that free radicals generated in excessive amounts due to cellular reactions or environmental factors (e.g., ozone, radiation or drug administration) may damage cell membranes. The free radical theory of aging, however, does not explain why some brain cells are more vulnerable to aging influences than others. Cells have a variety of mechanisms to protect the integrity of their deoxyribonucleic acid (DNA). Nevertheless, DNA damage can become fixed in the genome of a cell either as a genetic mutation or chromosomal aberration. The DNA replication theory states that aging may result from a gradual accumulation of random errors with eventual functional and/or reproductive death of individual cells. The absence of a generally agreed upon set of age-related changes in nervous system function has made it difficult to evaluate specific theories for aging in the nervous system. These theories, however, may indirectly apply to brain since the central nervous system interacts with and depends upon various other systems in the body.

No specific factor leads to aging in the central nervous system but a combination of deficits, imperfect compensatory mechanisms and undetected disease may ultimately weaken and lead to a loss of function. The central nervous system detects signals from the environment, and from within the body, and sends out signals that elicit proper responses. Unlike other tissues, brain cells operate in highly integrated networks. The total output must be meaningful, purposeful and ultimately adaptive in response to an ever changing environment. As described in the previous sections of this chapter, the nervous system can compensate for some losses that occur with age. When the contributions of disease or the compensations by mechanisms of plasticity are considered, few age-related changes are found to

occur. While the brain can compensate, at least partially, for some minor losses, less than perfect corrections may lead to computational errors and may predispose the system to further deficits.

Some deficits, either alone or in combination, make the system more vulnerable to further insults. With age there is an increased incidence of pathology. In many age-related disorders it appears that the pathological characteristics ofs disease are present in normal aging, although to a much lesser degree. For example, the neuropathological changes that occur in Alzheimer's disease differ quantitatively but not qualitatively from usual aging. It is reasonable to assume that there are some subtle neurochemical deficits which are ultimately followed by distinct pathology. It is not known, however, whether individuals that age successfully escape most pathology.

Thus aging of the brain may result from a cumulative set of errors which ultimately lead to critical functional losses. In most systems there are probably weaks links in this chain of events where some losses may be more crucial than others. Losses may become particularly important when they are compounded. According to this notion, highly adaptative or plastic systems will be particularly susceptible to age-related losses. It is possible to illustrate the way deficits can cause loss of function by examining the role of the hippocampus in learning and related functions.

As previously discussed, cholinergic function is partially reduced with normal aging and these losses are even more extensive in Alzheimer's disease. Aged rodents have deficits in learning the Morris water maze (see previous section). One weak link in hippocampal function, which leads to learning difficulties, might be a loss of cholinergic function. Thus, restoring cholinergic function might reverse deficits in hippocampal function. To test this hypothesis, fetal cholinergic neurons were transplanted into the hippocampus of aged rats [20]. Performance by behaviorally impaired aged rats that received cholinergic transplants was significantly better than pre-transplant rodents. This suggests that the original learning deficit was not due to a global "aging mechanism" but rather a specific loss in a particular brain area and neurotransmitter system.

The precise mechanisms for the age-related decline in cholinergic function is unknown; however, trophic factors may be important. Trophic factors play a key role in development and cell death. Thus, they may be fundamental for the maintenance and repair of the injured or aged brain. The finding that axonal and dendritic sprouting occurs with age suggests that trophic mechanisms are operational, at least to a degree, since regenerative growth occurs until very old age. Cholinergic neurons appear to depend on nerve growth factor (NGF) for their trophic support. NGF levels and NGF receptors may decline by as much as 50% with aging which may underscore the potential role for such factors by making select systems more vulnerable in old age.

Cholinergic neurons also participate in plaque formation which may further reduce function. The initial formation of a plaque may be part of a sprouting response to compensate for cell loss [22]. Axon sprouts from cholinergic neurons appear to grow into the plaque as it develops. Neuritic plaques may originate from an abnormal sprouting reaction due to a local accumulation of neurotrophic molecules and generation of substrates that promote growth. Thus, sprouting which can potentially rebuild and strengthen partially damaged circuits may eventually contribute to age-related pathology. Amyloid accumulation may also be produced as a product of aberrant regeneration. The levels of ß-amyloid mRNA are very high in hippocampal fields where sprouting is robust and plaque formation is most abundant.

In the hippocampus not only is cholinergic function decreased with aging but some intrinsic cell groups also appear to be lost. Cell loss may not be due to aging per se but perhaps to an interaction with the environment. It has been shown that prolonged (e.g, three months) exposure to glucocorticoid produces a loss of specific hippocampal neurons (e.g., area CA3) with concentrations of glucocorticoid receptors. In addition, within the population of the remaining cells, there are shifts in cell size so there are more small neurons (Fig. 9). Rats treated chronically with glucocorticoids show shifts in CA3 neuron size similar to those observed in aged rats [23].

Loss of some CA3 neurons produces more damage when individuals are subjected to further stress. Circulating glucocorticoids feedback onto the hippocampus to inhibit further steroid release from the adrenal gland. After hippocampal injury, steroid release is greater, since the hippocampal feedback inhibition is reduced; this causes more damage due to increased steroid levels. Glucocorticoids can also retard axonal sprouting so compensation is further reduced. These data

suggest that an age-related loss of CA3 neurons could be due to cumulative exposure to corticosterone, perhaps exacerbated by stress-related events. Thus, environmental factors may interact with the aging process in an auto-destructive cascade.

Small losses may be more critical when they occur in highly overadapted systems. Ultimately, too many corrective mechanisms may cause more massive losses. Cholinergic deficits alone may be insufficient to reduce behavior but in combination with cell loss may lead to decreases that are greater than each individually. In the hippocampus, cholinergic synaptic transmission enhances the action of excitatory pathways. Thus, loss of intrinsic excitatory neurons, plus the mechanisms that augment their firing, may compromise the fine tuning of adaptive responses necessary for higher function.

While some factors may decrease lifespan other environmental influences may prolong it. Caloric restriction has been the most consistent method of extending life span in the laboratory animal. In the B6 mouse strain a reduction in body weight of 8 grams leads to an increase in life span by about 6 months (Fig. 10; [24]. Reduced food intake can retard age-related changes in kidney function, fat metabolism, muscle mass and decrease the incidence of spontaneously produced tumors. Dietary restriction also reduces brain serotonin levels, prevents age-related losses in striatal dopamine receptors and improves maze learning performance in aged rats. While the precise mechanism(s) for the effect of dietary restriction on extending life span remains to be discerned, it is interesting to note that reduced food intake leads to atrophy of the pituitary gland and diminished levels of pituitary hormones.

Aging studies require that careful attention be given to the subject selection and use of models. As discussed in this chapter, the conclusions that are drawn depends markedly on subject selection. It is clear that literature on aging research can be quite contradictory and confusing in its own right. Heterogeneity may be inherent factor in aging studies; however, it may also result from problems due to experimental design. All aging studies generally make assumptions about methods, subjects and the aging process which need to be considered when interpreting the literature and designing experiments. Differences in these parameters between laboratories can often alter the conclusions. Currently the rate of aging is expressed chronologically although this is recognized as a relatively weak marker of physiological age since many individuals age at different biological rates. How old is old? Rodent strains most commonly used for aging studies live for over two years and have a maximum lifespan of about 30 months (Table 1). A rat of 25-30 months would be considered aged. Many investigators even disagree on when development ends and aging begins. dA rat is not mature until approximately 3 months.

Rodents raised in a standard vivarium may have been exposed to various diseases. In order to circumvent the potential problems associated with disease, the National Institute on Aging maintains a colony of aged rodents reared in germ-free environments. These animals are referred to as barrier raised. When rodents are reared in home colonies, information should be provided as to the breeding conditions used to produce the stocks, the health of the colony, the diseases to which they have been exposed and the expected lifespan of the strain. Some aged rat strains need to be studied with caution. For example, aged Sprague Dawley rats have spontaneously produced pituitary tumors and become obese with aging. Fischer 344 rats have been used more extensively; however, they are prone to testicular tumor formation. The use of a single inbred strain does provide some "genetic control", although the results may not be general to the species as a whole. Furthermore, single strain studies do not adequately assess potential genotypic contributions to age-related alterations.

Autopsy tissue provides an approach to study the aged human brain. The study of the aged human central nervous system is an exciting and expanding area of research made feasible by the increased availibility of autopsy tissues. Brain tissues from normal aged and subjects with age-related disease are routinely collected by various "brain banks". Detailed clinical data which describe the conditions just prior to death are essential. For example, a pre-mortem condition known as the agonal state should be noted, since some patients that die in an agonal state suffer from respiratory or other problems which result in brain anoxia immediately prior to death. Some enzymes, transmitters, receptors and high abundance mRNA are suprisingly stable after

death so that autopsy tissues can provide useful and important information. However, many dynamic cell processes (e.g., calcium homeostasis) cannot be measured with post-mortem tissue. The study of more accessible peripheral tissues (e.g. cultured fibroblasts, lymphocytes) may help determine the general mechanisms that underlie the age-related alterations in the central nervous system as well.

Conclusion. The process of aging in the central nervous system is an interaction of age-related losses, disease and compensatory mechanisms which work to offset functional declines. While most studies emphasize age-related losses, many properties in specific systems are preserved (e.g. synaptic transmission in select brain pathways, oxidative cerebral metabolism, etc). Neurochemical research on aging needs to be considered in the context of specific functions and the parameters most critical for those functions. Heterogeneity is one of the hallmarks of aging. Any molecular theory needs to account for the heterogeneity that exists between individuals and even between cell groups in the brain. Adaptive or plastic mechanisms probably play a key role in maintaining functions during aging. Brain aging probably is not due to a single factor but rather a series of interdependent mechanisms that ultimately compromise the precision and computational accuracy of the networks. This would first appears as an inability to cope with extreme challenges once easily managed. The speed at which select cognitive and non-cognitive tasks can be accurately processed may slow as perhaps the brain needs more and more trials. Integrated multidisciplinary approaches appear essential in order to understand the process of aging. Indeed as we learn more about aging it may be possible to provide an understanding of how to optimize the potential to age successfully.

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Table 1. **Commonly used rodent strains for aged animal studies**

RODENT STRAIN	MAXIMUM LIFE SPAN	
	Male	Female
A/HeJ mice	18.6	15.3
Balb/c mice	24.4	23.3
CBA/CA mice	27.1	24.4
C57Bl/6 mice	25.6	25.6
DBA/2 mice	23.5	21.9
Fischer 344 rats	29.5*	

Values are expressed in months. These rodents are commercially available through Charles Rivers Breeding Laboratories which is under contract with the National Institute on Aging. Male and female rodents are virgins. *Rats housed 1 per cage have a mean life of 22.7 months; however, when housed 3 per cage it increases to 28.5 months (for review see 25).

FIGURE LEGENDS:

Figure 1. **Aged population as a percent of the total population.** Values represent the number of the elderly individuals (65 years of age or older) that are expressed as a percent of the total population. Source is the U.S. Bureau of the Census, *Current Population Reports*, series p-25 Nos. 311, 519, 614, 643 and 704. Data for years 1990 to 2060 are projections based upon series II fertility assumuption (2.1 children per woman, 400,000 nnet migration per years, slight mortaility decline).

Figure 2. **Aging leads to alterations in neuronal and glial cell populations.** Brains from a group of 51 individuals with normal cognitive function were used in this study. The brains were fixed and sectioned at 20 microns. After staining with cresyl violet, cortical cells were counted with a quantimet 920 [data are redrawn from 2].

A. Large neurons (>90 microns) show a strong negative correlation with aging in all the midfrontal, superior temporal and inferior parietal areas of the neocortex.
B. Small neurons (<90 microns but > 40 microns) increase in number with advancing age.
C. Glial cells (<40 microns) increase with advancing age.

Figure 3. **Decreased cell number in the substantia nigra in man as a function of age.** The number of neurons in the substantia nigra is plotted against increasing age. [data redrawn from 3].

Figure 4. **Changes in granule cell dendritic length with increasing age.**

A. Total dendritic length per human dentate granule cell. The age-related changes are statistically significant [data redrawn from 7].
B. Representation of reduced competition for an afferent suppply consequent to the death of a neuron which then leads to dendritic proliferation by surviving neurons.
C. The surviving neurons increase their dendritic branching to fill in the areas vacated by the dead neuron. Astrocytes may increase their production of growth promoting agents as they become reactive.

Figure 5. **Neuromuscular junction during aging.**

A. Neuromuscular junction from a young and an aged rodent. Note the increased number of branches and longer terminals in the aged rodent.
B. Total acetylcholine release.
C. Acetylcholine released per nerve terminal. The values are the means ± SEM [data are redrawn from 10].

Release of acetylcholine was evoked from a rat hemidiaphragm nerve preparation. The hemidiaphragm and phrenic nerve were isolated from young (10 months of age) and old (28 months of age), male and female, Fisher 344 rats. The stimulus (1, 10 or 20 Hz) was delivered for 15 min.

Figure 6. **Cytosolic free calcium decreases with aging.** Cultured skin fibroblasts from young (21 years) and aged (61 years) donors were used in these studies. Cytosolic free calcium was determined with the calcium sensitive fluorescent dye, Fura 2 in serum deprived skin fibroblast from normal healthy individuals. The cells were examined at early passages to avoid complications due to *in vitro* aging. [data from 16].

Figure 7. **Cerebral metabolic rate for glucose as a function of increasing age.** Glucose utilization was measured by positron emission tomography with fluoro-2-deoxyglucose in carefully screened healthy individuals (aged 28-83 years). Values are expressed as the rate of glucose metabolized (mgs) per 100 grams of tissue per min. [data redrawn from 17].

Figure 8. **Changes in cell size populations during chronic glucocorticoid treatment and normal aging.** The chronic group represents rats (8 months old) that were treated for three

months with glucocorticoids (5 mg per day). The aged group were male Fisher 344 rats aged 28 months. The outlines of all the cells that contained nuclei were traced and the cell area was then determined by a computer area program. The areas of the cells in the first 200 microns of the CA3 region, after the CA2-CA3 border, were calculated. Values are the mean ± SEM, n=3 per experimental group [data replotted from 23].

Figure 9. Performance of young and old rats on the Morris water maze task. Non-barrier raised retired breeder female Sprague Dawley rats were used in these studies. Seventy five old (21-23 months of age) and thirty-one young (3 months of age) rats were screened to select for rats with impaired and non-impaired performance. The water maze was a circular tank (140 cm diameter and 45 cm deep). The pool was located in the corner of a room filled with numerous extra maze cues that were available for the rats to use in locating the escape platform. The pool was filled to a depth of 30 cm and water was made opaque by the addition of powdered milk. The aged animals showed a wider range of performance scores that that of younger animals. Some of the old rats performed as well as the young rats [data are redrawn from 20].

Figure 10. **Dietary food restriction prolongs survival.** Mice were maintained on a diet of restricted food intake, without malnutrition, starting at 12 months of age.

A. Body weight of B6 mice fed *ad libitum* or a restricted diet. Mature B6 mice on the restricted diet stabilized at about 25 grams after 2 months of underfeeding. Weights are plotted as the means for all mice alive at the indicated ages.

B. Survival of B6 mice. Each point in the survival curve represents one mouse. Mean survival was 24.9 ± 0.9 months for all of the B6 mice fed *ad libitum*, as opposed to 29.9 ± 1.4 months for the B6 mice fed a restricted diet. Mean survival for the longest lived 10 percent of each B6 group (n=3) was 31.5 ± 0.5 months for *ad libutum* and 38.2 ± 1.4 for the restricted diet groups, respectively [data are redrawn from 24].

Fig. 1

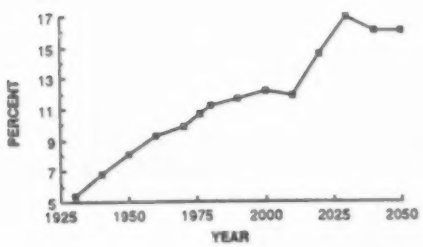


Fig. 2

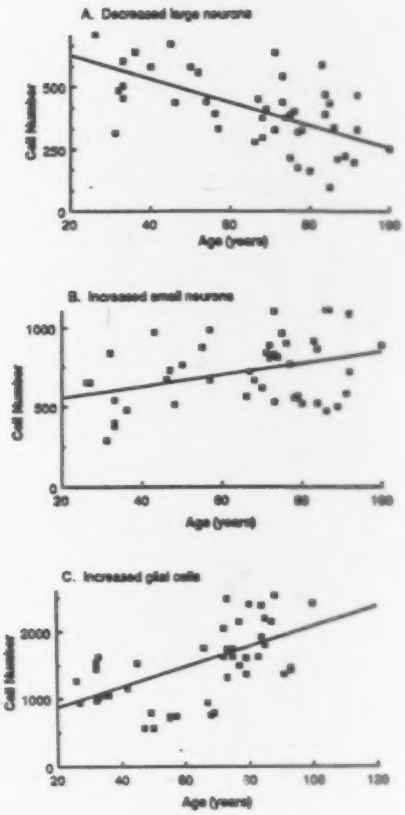

A. Decreased large neurons
Cell Number
500
250
0
20
40
60
80
100
Age (years)
B. Increased small neurons
Cell Number
1000
500
0
20
40
60
80
100
Age (years)
C. Increased glial cells
Cell Number
2000
1000
0
20
40
60
80
100
120
Age (years)

Fig. 3

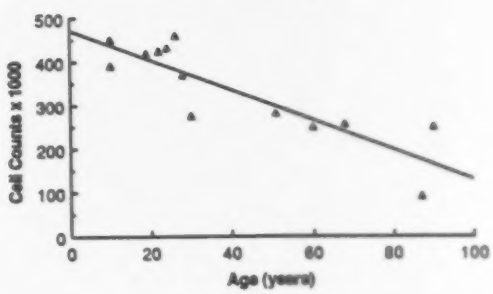

Cell Counts x 1000
500
400
300
200
100
0
0
20
40
60
80
100
Age (years)

Fig. 4

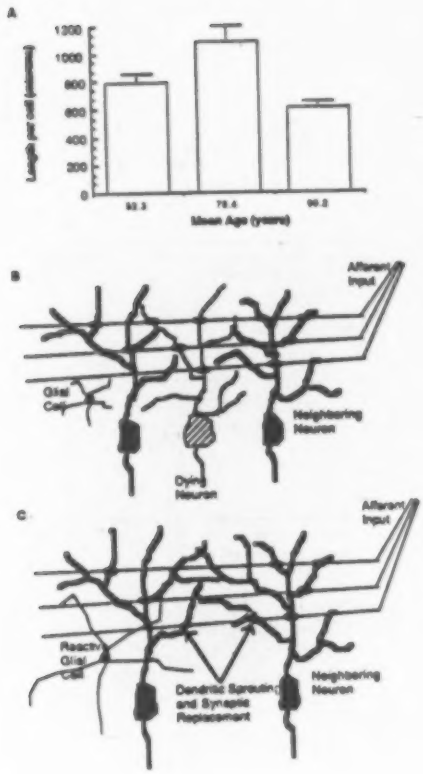

A
1200
1000
800
600
400
200
0
Mean Age (years)
B
Afferent Input
Glial Cell
Neighboring Neuron
Dying Neuron
C
Afferent Input
Reactive Glial Cell
Dendritic Sprouting and Synaptic Replacement
Neighboring Neuron

Fig. 5

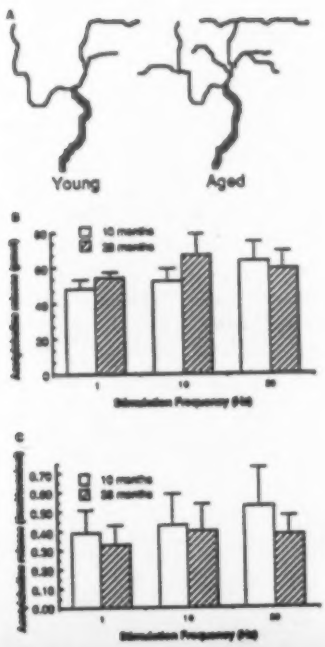

A
Young
Aged
B
10 months
30 months
C
10 months
30 months

Fig. 6

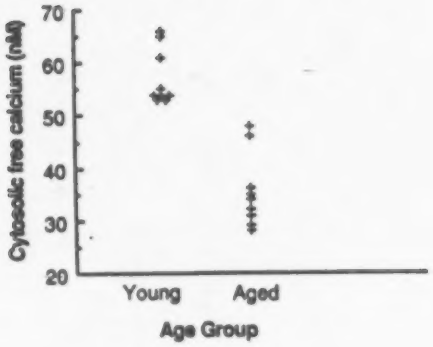


Fig. 7

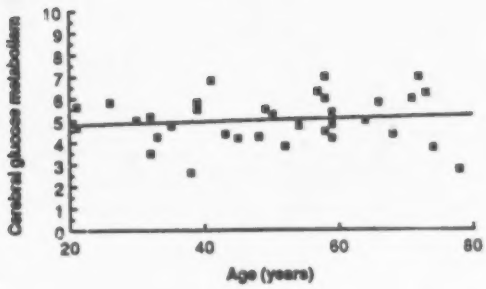


Fig. 8

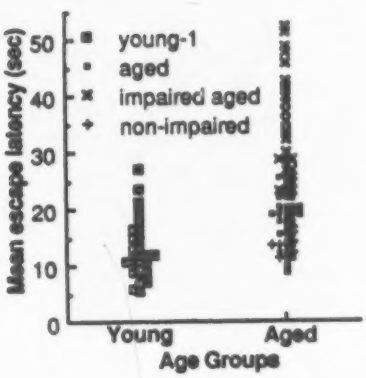


Fig. 9

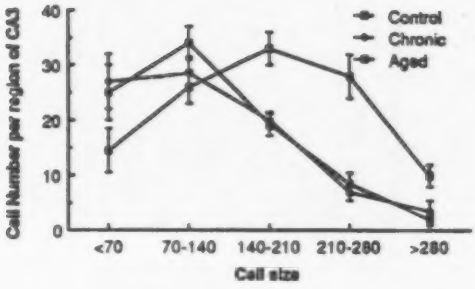
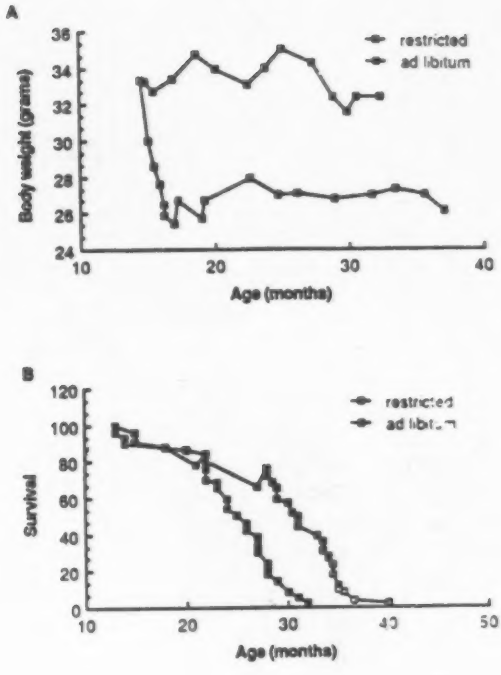

Control
Chronic
Aged
Cell Number per region of CA3
0
10
20
30
40
<70
70-140
140-210
210-280
>280
Cell size

Fig. 10


A
restricted
ad libitum
Body weight (grams)
24
26
28
30
32
34
36
10
20
30
40
Age (months)
B
restricted
ad libitum
Survival
0
20
40
60
80
100
120
10
20
30
40
50
Age (months)